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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 16 1954

THE CHANGING AETIOLOGY OF HEART DISEASE*

BY

W. MELVILLE ARNOTT, T.D., M.D., F.R.C.P.

William Withering Professor of Medicine, University of Birmingham

Until very recently it was customary to classify heart disease under such structural headings as "aortic incompetence," "mitral stenosis," or "pericarditis." The last few decades have seen the development of knowledge of disordered function as well as of structure. The most satisfactory classifications of disease are those which are based on causes, for the good reason that effective prevention depends on knowledge of aetiology. At once, of course, one is up against the problem of multifactorial causation. There are few disease processes that can be assigned exclusively to a single cause. The *Treponema pallidum* is essential for the production of syphilitic aortitis, but it is only a small minority of those infected who develop aortitis. There must be other factors which determine localization of the organism in the aorta. The famous razor of the great Franciscan philosopher William of Occam, which runs somewhat as follows; "Entia non multiplicanda praeter necessitatem," is a useful intellectual tool to use initially but little more, as to reach anything approaching a satisfactory solution it is usually necessary to invoke many causes.

Turning now to heart disease as it presents to-day, it is obvious that three types predominate; these are rheumatic heart disease, ischaemic heart disease, and hypertension, the latter two frequently combining to cause disability and death, and possibly sharing some causal factors. This is true at any rate up to the age of 70, but at greater ages the Registrar-General reports that a high proportion of deaths are certified as due to myocarditis and myocardial degeneration. Not enough is known to say whether these are due to cardiac ischaemia or are the result of some much more subtle disorganization of biochemical function concerned with senescence. Before considering the rheumatic and ischaemic groups in more detail let us briefly look at some less prominent forms of heart disease.

Pulmonary heart disease is a more important cause of disability and death than is generally realized. It does not receive adequate recognition in the Registrar-General's returns, as the cause of death is usually, and quite reasonably, ascribed to bronchitis, emphysema, pneumonia, or status asthmaticus. The mechanism in these conditions is pulmonary hypertension caused by rigidity and obliteration of the pulmonary vascular tree, which robs it of its capacity to dilate sufficiently to allow the passage of a large volume of blood without elevation of pressure. This rigidity is due partly to structural change in the vessel walls and partly to low alveolar oxygen content. Fundamentally, the prevention of this form of cardiac disability must await better knowledge of the causation and prevention of bronchitis, bronchiectasis, emphysema, etc. Thyrotoxicosis presents no great cardiac problem, as there are several ways of correcting hyperthyroidism. Syphilitic heart disease is now rare in this country, and theoretically there is no reason why it should not become extinct. There are signs that congenital heart disease, inaccessible as the problem seems, may prove susceptible to preventive measures—such as the avoidance of maternal virus infections in the early stages of pregnancy and of foetal anoxia at delivery (Record and McKeown, 1953).

*From a lecture given to the Abernethian Society at St. Bartholomew's Hospital, March 19, 1954.

Rheumatic Heart Disease

Numerically, the only important cause of heart disease below the age of 40 is rheumatism. A remarkable change has taken place in the incidence of rheumatic fever (using the term to include acute rheumatism) during the course of this century. There has been a steady decline in the incidence of the acute rheumatic manifestations—so much so that as long ago as 1930 Glover stated that rheumatic fever was an obsolete disease. Its mortality in 1940 was, at all ages, of the order of 25% of the rate at the beginning of the century, while in 1950 the rate was only half that in 1940. There has been an equally dramatic fall in deaths from rheumatic heart disease in people below the age of 20. This is not surprising, as it is only the most severe forms of rheumatic heart disease, usually associated with florid acute rheumatism, that kill so soon.

It is not easy to assess the relevant mortality from rheumatic heart disease in older individuals, as several changes in methods of classification have made it difficult to get comparative figures from the Registrar-General's returns. However, there is probably a moderate decrease, so that the rate for 1936–8 is approximately 75% of that for 1921–3 (Knowelden, 1949). A curious feature, however, is that most of this decline is in males, the rate for females having dropped comparatively slightly. It has to be remembered that rheumatic heart disease lasts on the average about twenty-five years, with extremes of from a few months to many decades. This means that, supposing a method were discovered now absolutely preventing acute rheumatism, the full effect on the death rate from chronic rheumatic heart disease would not occur until about 1980. In this respect it is not inappropriate to recall

the belief current twenty-five years ago concerning the effect of arsenical therapy in syphilis. It was taught then that, whereas arsenic was effective in primary, secondary, and tertiary syphilis, it was comparatively ineffectual in preventing the late neurological complications, dementia paralytica, and tabes dorsalis. The fallacy in this belief was that these late forms occur some twenty to thirty years after the primary infection, and as arsenical therapy was not widely practised until after about 1915 its full effect could not be assessed until about a quarter of a century later. As a matter of fact, from the mid-thirties onwards there has been a striking decline in their incidence fully comparable with that in tertiary forms of syphilis.

Aetiology of Acute Rheumatism

Let us now consider what is known of the aetiology of acute rheumatism and its attendant heart disease, with the particular object of recognizing factors which may account for this decline in incidence and of deducing what should be done to minimize or entirely prevent its recurrence. In this I am greatly indebted to D. A. Long, whose Milroy Lectures on the pathogenesis of rheumatic fever have just been published (1954). It has long been recognized that acute streptococcal infection of the tonsils and upper respiratory tract plays a very important if not an essential part in originating rheumatic fever. Some have believed that such infections act as non-specific provocatives which incite the rheumatic reactions in susceptible subjects. This conception allows rheumatism to develop in other forms of injury in the absence of streptococcal infection. Workers such as Coburn (1931), Swift (1949), and others regard rheumatic fever as a specific reaction to infection with the group A haemolytic streptococcus. The weight of evidence supports this latter contention. Long considers that the bacteriological and immunological evidence that haemolytic streptococci cause rheumatic fever is at least as good as that suggesting that haemolytic streptococci cause scarlet fever.

Scarlet fever has declined both in incidence and in severity during the past fifty years, particularly so during the last fifteen. The reasons for this reduction in streptococcal infection are complex, but they probably include many aspects of the steady improvement of living conditions during this period. So far, no clear case has been made that any particular aspect of environment plays a dominant part in this change. Respiratory tract infections are contact infections, and one would expect them to be closely dependent upon crowding. The evidence, however, for this is conflicting, as the decline continued throughout the period of unparalleled overcrowding during and after the war. This does not invalidate that hypothesis, as other factors, such as antibiotic therapy, may have cancelled it out. Virtually all antibiotics are very effective against the haemolytic streptococcus, and the development of antibiotic resistance by this organism is uncommon. There is much evidence to support the belief that such prompt treatment of streptococcal infections minimizes the risk of acute rheumatism and that the prophylactic use of either sulphonamide or penicillin in those who have had rheumatism significantly diminishes the rate of relapse.

Recent studies (with adequate controls) by Wannamaker *et al.* (1951) on large numbers of sufferers from streptococcal tonsillitis in an American Army camp demonstrated conclusively that rheumatism was almost entirely prevented by prompt treatment with penicillin. In fact, at the present time, the most useful procedure aimed at preventing rheumatism and rheumatic heart disease is the treatment of tonsillitis by sulphonamide or penicillin. There is no need to await bacteriological proof that the tonsillitis is streptococcal in origin, as, apart from diphtheria, the other causes of exudative tonsillitis are unimportant, consisting in the main of the occasional case of glandular fever or Vincent's angina. The development of oral preparations of penicillin of a potency sufficient to achieve in most people blood concentrations that will deal with all but the most severe streptococcal infections are a great help in this respect. It must also be remembered that the sulphonamides are highly effective against the streptococcus. I believe that if such prompt treatment of tonsillitis were extensively practised there is a reasonable prospect that rheumatic heart disease would in a quarter of a century be as rare as syphilitic aortitis at the present day. Sulphonamide and penicillin occasionally cause sensitivity reactions, but these seem to me trivial risks compared with the benefit that may well be achieved.

What a transformation would be effected if rheumatic heart disease, with its toll of life and liberty during the first half of life, could be banished for ever. I sometimes think that cardiologists, as individuals and collectively in their societies, have not devoted as much interest and enthusiasm to this object as it deserves. The explanation may well be that exploration in this field demands the outlook and techniques of a bacteriologist, immunologist, and social scientist. These are all fields which those of us brought up as conventional cardiologists are ill equipped to explore.

Group A Streptococcal Infection

Turning now from the seed to the soil, what determines the rheumatic reaction in sufferers from group A streptococcal infection? I suppose at one time or other almost everybody is infected with this organism. There is no good evidence that any particular member of group A produces a specific substance causing rheumatism. All the evidence points to some general property of the group which initiates the disease in a susceptible person. The infection must persist for some little time, perhaps as long as two to three weeks. There is much evidence that the cellular injury which determines the rheumatic reaction is the result of a reaction between the circulatory antigen derived from the streptococcus and a fixed antibody. D. A. Long marshalled evidence strongly in favour of regarding this reaction as similar to the bacterial allergy seen in tuberculosis. For instance, the response is delayed and can be passively transferred with cells; histamine plays only a minor part (hence the inefficacy of antihistaminics) and the reaction can be suppressed by cortisone. The factors which determine the sensitivity are not understood, although clues are by no means lacking. There is much to support the belief that interference with the chemical structure of collagen is important.

The relationship to ascorbic acid metabolism is not fully explored. For instance, there is no satisfactory explanation why sufferers from rheumatism, rheumatic fever, rheumatoid arthritis, and active tuberculosis can absorb large quantities of ascorbic acid without reaching saturation point. It is known that certain amino-acids are essential to normal antibody production; rheumatic fever is seldom associated with diabetes mellitus; there is some obscure association between thyroid dysfunction and rheumatic fever. These and many other clues point to disorders of tissue metabolism, perhaps inborn, as being at the basis of rheumatism. Such a conclusion does not mean very much, as similar general phrases might be used to cover many pathological reactions.

Coronary Heart Disease

This disease is not unknown in the third decade, occurs occasionally in the fourth, is quite common in the fifth, and exerts a heavy toll in the sixth and seventh decades. There is abundant evidence that in the last 30 to 40 years it has increased to an extent much greater than can be attributed to such factors as the changing age structure of the community and the increased awareness of the clinical and pathological features of coronary occlusion.

The evidence which supports this absolute increase comes from many sources. The standardized mortality from "diseases of the coronary arteries and angina pectoris" has almost doubled (Morris, 1951). Morris also analysed the incidence of spontaneous rupture of the heart in the records

of coroners' necropsies and found an increase of more than twofold from 1932 to 1949. This is a particularly impressive item of evidence, as this gross pathological lesion allows of no error in reporting and coronary infarction is virtually its only cause.

There is the evidence of the clinician. Ryle and Russell (1949) record that Osler was admitted to the Fellowship of the Royal College of Physicians before he had seen a case of angina pectoris in hospital or private practice, while Sir James Mackenzie, in 1923, two years before he himself died of a coronary occlusion, stated that only 380 patients had consulted him for angina pectoris. The first clear account of the clinical picture of coronary thrombosis in England was by Sir John McNee (1925). Nowadays the life of a cardiologist is literally dominated by ischaemic heart disease.

The present high morbidity and mortality of this disease is unusually striking, because it has a much greater incidence in the professional classes, in particular the medical profession, although this high incidence is in varying degree general throughout the occupations of the Registrar-General's Class I. For instance, the standardized mortality ratio of deaths from coronary disease among physicians and surgeons is 368, as compared with less than 40 among coal-miners, quarriers, and agricultural labourers.

The magnitude of the menace was emphasized by the study Morris *et al.* (1952) made of coronary heart disease in general practitioners. They made use of the records of the Medical Sickness, Annuity and Life Assurance Society, which covered clinical coronary heart disease diagnosed among 6,000 medical men aged 35–64 holding "immediate benefit" non-cancellable sickness insurance policies. The data indicate that a medical man under 45 years of age who has not yet had any coronary disease has a one in five chance of developing it before the age of 65, and a one in fourteen chance of dying of it before that age.

Another factor which must be considered is that the disease is occurring in younger people, although it remains very uncommon in women before the menopause and is at all ages less common in that sex.

The problem, then, is to isolate the important factors which lead to ischaemia of the heart muscle; ischaemia which frequently results in necrosis of the myocardium with fatal shock, arrhythmia, or ventricular rupture—an event which is commoner as age advances and in males in the "upper," especially professional, classes, and which has increased several-fold in the last generation.

Approach Through Morbid Anatomy

Let us first of all approach the problem along the road of morbid anatomy. The crucial event here seems to be the occlusion of a coronary vessel of such size as to cause muscle ischaemia that is beyond the aid of collateral circulation. I am aware that it is not established that structural vascular occlusion always occurs—in fact, it is quite possible, even likely, that an identical lesion of the muscle occurs without demonstrable occlusion, but this is uncommon. This critical blockage is usually due to a clot; and here at once we confront a complicated situation. The mechanisms whereby blood clots—or avoids clotting—are imperfectly understood. Much emphasis has been placed on coronary atheroma as the determining factor, but too much weight must not be attached to this alone. Duguid (1954) advances impressive evidence in support of the hypothesis that atheroma is the result of a thrombus having formed on the vessel wall. Morris (1951) has considered the place of atheroma in some detail, starting from the very reasonable assumption that if it is the principal cause then its severity in the coronary vessels should have increased proportionately to that of coronary occlusion. He has made use of the admirable records of the London Hospital Institute of Pathology, which extend back far enough to make it possible to compare the first decade of this century with the fifth. Calcification, about the presence of which there can be little dispute, was taken as the "touchstone" of atheroma.

Some 6,000 reports from 1907 to 1949 were studied, relating to both sexes and to ages 30–69 inclusive. While the number of cases of coronary heart disease showed a sevenfold increase over this period, advanced coronary atheroma showed a substantial decrease; this was seen in all the sex, age, and pathological categories (including hypertensive) studied. Although this inverse correlation between the frequency trend of ischaemic heart disease and that of coronary atheroma makes it unlikely that the latter is the principal factor in causing coronary occlusion, it may yet be a common denominator in the process. Perhaps calcification does not reflect adequately the incidence of atheroma in that it may be a less common feature of that condition, which itself is increasing. Much remains to be done in this field, in particular the development of some satisfactory quantitative method of measuring the extent of atheroma, ideally during life but at least at necropsy.

The Problem of Atherosclerosis

The last few years have seen a revival of interest in the problem of atherosclerosis, particularly in connexion with the level and control of the cholesterol content of blood. The precise significance of the cholesterol that is found in atheromatous lesions is unknown. Opinion ranges from regarding it as the cause of atheroma to relegating it to the role of an incidental deposit in tissues already injured. It can safely be said, however, that there is an important relationship between the concentration of cholesterol in the serum and the development of atherosclerosis (Keys, 1952).

Great play is made of the fact that if rabbits or chickens are given a diet containing an enormous amount of cholesterol extensive aortic atheroma follows within a few months. This observation may not have a very wide significance, as neither of these species normally eat much cholesterol, its only dietetic source being dairy produce and animal fat. In the dog, feeding a large amount of cholesterol produces atheroma only if combined with induced hypothyroidism; while in man it has been found impossible to influence the level of blood cholesterol merely by changing its dietetic level. This is hardly surprising in view of the fact that cholesterol is so easily broken down and synthesized in the body. The one point that is clear is that the level of blood cholesterol in man is not influenced by the cholesterol content of diet. Yet dietetic factors other than cholesterol play a very important part in determining its level. This can be raised by a diet which contains a high proportion of fat, or which, while not containing so much fat, has a calorie content considerably above energy requirements.

This susceptibility of the serum cholesterol to these nutritional factors becomes apparent only after the age of 30: it seems as if prior to that age there is some homoeostatic mechanism which holds cholesterol content within narrow limits. Keys *et al.* (1952) have demonstrated these relationships very beautifully in their surveys of serum cholesterol levels in comparable groups in Minneapolis, London, Naples, and Madrid. They have also emphasized the important regression of serum cholesterol content on age. A figure that would be normal at the age of 60 would be abnormally high at 20; in fact the essential basis of clinical deduction from blood cholesterol estimations is a knowledge of the normal of the particular community concerned and its variability in relation to age and sex.

It appears, then, that after the age of 30 the "better" the diet the higher the blood cholesterol.

The word "better" in this context has, of course, a meaning based on the popular belief that the more dairy produce and animal food one eats the greater the benefit. In fact, dairy produce is sometimes classed as "protective" food in the sense that its vitamin content is supposed to raise resistance to pathogenic micro-organisms. While deficiency of these foods undoubtedly means serious malnutrition, excess may spell dangers of a quite different sort. Popular belief is very understandably biased by the sensuous pleasure derived from eating dairy and animal food.

Blood Cholesterol and Ischaemic Heart Disease

Now what is the relationship of blood cholesterol level and ischaemic heart disease? However one views the problem there seems to be a close positive correlation between these two variables. Whether one compares nations or groups within nations, the statement, "The 'better' the diet the higher the serum cholesterol of middle-aged males and the more coronary disease," seems to hold good. Coronary heart disease is one of the main causes of disability and death in the United States, Canada, Britain, Northern Europe, Australia, and New Zealand, and these are all countries which, nationally speaking, derive more than 30% of the food calories from fat. On the other hand, areas like Southern Europe, Africa, India, and the Orient in general have diets the fat of which contributes less, usually much less, than 20% of the calories. It is difficult to be certain that atheroma and coronary heart disease are much less in these countries. The extent and standards of medical, biochemical, and pathological work are, generally speaking, much inferior, while the vital statistics of the populations at risk are less clearly defined. Nevertheless, while the evidence is not of the same quality as in the materially more favoured countries, it is uniformly consistent with the conclusion that the diseases are comparatively very uncommon.

In man, certain disorders such as diabetes mellitus, myxoedema, and obesity are often associated with prolonged elevation of blood cholesterol and also with a high incidence of atherosclerosis and associated arterial occlusion and ischaemic heart disease. The rare disorder of "familial idiopathic hypercholesterolaemia" shows a high rate of ischaemic heart disease. Lastly, persons who have ischaemic heart disease as shown by definite angina pectoris or infarction tend to have higher serum cholesterol values than otherwise comparable people (Geier, 1949).

On the other side of the picture there is a general impression that sufferers from chronic intestinal disease of the malabsorptive type—for example, steatorrhoea—have low levels of blood cholesterol, scanty atherosclerosis, and little liability to ischaemic heart disease.

Circulatory Disease in the War Years

Another curious piece in this mosaic of causalogy is provided by the changes that occurred in the death rate from circulatory disease in Norway during the period from 1940 to 1945, when the country was occupied by the Germans (Strøm and Jensen, 1951). Within a few weeks of occupation there was a substantial decline in all forms of circulatory disease presumed to originate in arteriosclerosis; conversely, the upward trend of incidence of these diseases was resumed within a similar period after the termination of enemy occupation. Now, the period in question was naturally associated with many important changes in the environment of the population, among them being a reduction of the average daily food intake per head from 3,470 calories to 2,850, with a reduction in fat from 159 g. (37% calories from fat) to 71 g. (20% calories from fat). It was also noted that there was a concurrent reduction in the thrombo-embolic complications of major surgical operations in the large hospitals (Dedichen *et al.*, 1951). These changes are compatible with the hypothesis that abundant fat intake favours vascular occlusion, but it is difficult to understand how the effect of the changes could be so soon apparent unless one supposed that they alter the coagulability of the blood. This latter possibility is intriguing, and stimulates speculation.

It is more than likely that alteration in blood coagulability plays just as important a part as atheroma of the vessel wall in promoting coronary thrombosis. Liability to post-operative thrombophlebitis shares with coronary heart disease a background of later life, obesity, and a chronic low level of physical activity. If this be proved to be a substantial factor there is a prospect of favourably altering the course of established ischaemic heart disease by appropriate measures. In brief, repentance even late in the day may be rewarded by some remission of sentence.

The increase in incidence of ischaemic heart disease might be attributed to the improving nutritional status of the community, as it is beyond dispute that malnutrition in North America, Northern Europe, etc., has steadily decreased until it is now of negligible proportions. Yet one would expect that it would be accompanied by an approximation of incidence in the various classes. Of that there is as yet no sign, and there has been no increase in the nutritional status of the professional classes themselves, rather the reverse. One will watch with interest the mortality experience of coal-miners in this respect, as the last ten years has seen an outstanding improvement in their economic position and there is now no financial reason whatsoever why they should eat less of the relatively expensive "fat foods" than the professional classes.

Influence of Physical Activity

Reverting to the occupational incidence of ischaemic heart disease, it was pointed out by Stocks (1951) that a sedentary mode of life might be a predisposing factor. It is obvious that among the many differences that distinguish the professional and labouring classes is that the latter often earn their living by the sweat of their brow, while the former are in the main "chairborne." This factor has been the subject of an outstandingly able investigation by Morris *et al.* (1953). They studied the morbidity and mortality due to ischaemic heart disease in drivers and conductors employed in the London buses and underground railway, the postmen, telegraph operators, telephonists, etc., in the London postal area, and most of the established men in the executive and clerical grades of the Ministries served by the Treasury Medical Service (Registrar-General's Occupational Grades II and III).

The essence of the results was that there was a significantly higher incidence of fatal coronary disease in the "inactive" occupation groups—that is, drivers as compared with conductors, telephonists with postmen on the delivery round, etc. It seemed, however, that the incidence of angina pectoris was rather higher in the active group; this, taken in conjunction with the better mortality experience of that group, meant that heavy workers tended to have coronary disease in a more benign and chronic form than light workers, and to die more commonly in second or later episodes of the disease. Although the two groups seemed, apart from the amount of exertion in their work, to be in all respects comparable as regards social class, implying similar dietetic, recreational, and other habits, the additional precaution was taken of analysing the 67 deaths of married women from coronary disease obtained from the same source. These when grouped according to the husband's occupation showed no group difference, thus emphasizing that the cause of the difference in mortality experience of the husbands lay in their occupational environment rather than in their home life.

Psychological Factors

Psychological "stress and strain" has for long been popularly believed to play an important part in a wide variety of diseases, including ischaemic heart disease and essential hypertension. So far as I can see, this hypothesis has no scientifically credible basis whatsoever—in fact, most of the evidence adduced in its support is dubious and much of it absurd. The argument runs somewhat as follows. Ischaemic heart disease is steadily increasing in frequency in the technically more highly developed and therefore wealthier countries, and in these countries it affects principally the professional, executive, and managerial classes; therefore there is some factor inherent in such people, or in their environment, which favours this disorder. So far the argument is irrefutable, but it then proceeds to select as important in this respect the concept that this lethal influence consists of (*a*) the exacting character of sustained

mental work accompanying intellectual occupations and posts involving heavy responsibility; (*b*) the emotional tensions that frequently accompany business, professional, and intellectual life; and (*c*) the inheritance of an ambitious or conscientious personality pattern. To sustain this argument it is necessary to show that these factors are much more potent in the affected classes. This has never been done; indeed, I believe (without scientific proof) that a dispassionate consideration of the matter exposes the concept as a fantasy of wishful thinking.

The reverse of the argument implies that the labouring classes in the wealthy countries and the great majority of the agrarian inhabitants of the Orient live some sort of idyllic existence, close to the soil, securely insulated from the fierce competitive, intellectual, and emotional burdens which grind the life out of those unfortunates whose lot it is to think, direct, and govern. It seems to me more likely that the stress factor operates in the reverse direction. The life of a physician in Birmingham is surely much less stressful than that of a peasant in the Yangtse Valley, with the ever-present menace of flood, famine, pestilence, and war; or of the tribesman in Equatorial Africa tortured by the taboo and sanction of primitive belief, to which are now added the tensions of organized political agitation. To subscribe at all to this factor one has to believe that the capacity to "feel" emotionally, to think deeply, to love, to hate, to fear, to hope, to aspire, and to despair are all much more highly developed in these materially favoured classes who get ischaemic heart disease. Basically, the intensity of all these intellectual and emotional activities, however much custom and education may alter their outward manifestations, is probably fairly uniform throughout the human family. Surely if these were fatal influences war, with such catastrophes as befell Norway, would greatly aggravate ischaemic heart disease. All available evidence is to the contrary.

The ready acceptance of this "stress-and-strain" concept is very understandable. It nourishes the *amour propre* of the believer and it is readily acceptable to the unfortunate victim and his relatives. It places ischaemic heart disease in the position of being the unjust reward of virtue. How much nicer it is when stricken with a coronary thrombosis to be told that it is all due to hard work, laudable ambition, and selfless devotion to duty than to be told it is due to gluttony and physical indolence. I know of nothing that conclusively disproves this psychological stress-and-strain concept; my contention is that so far there is little to support it, and much that makes it unlikely.

Conclusion

In conclusion I must emphasize that I have only briefly considered three of the many possible factors underlying ischaemic heart disease. There are many others, such as heredity and the important part played by essential hypertension with all its complex environmental background. It is important to recognize that such studies as I have considered merely indicate significant (in the statistical sense) correlations, which must not be taken as proving a causal connexion. They merely show how measurable environmental factors vary in relation to the incidence of ischaemic heart disease. It is easy to establish similar significant correlations with innumerable other factors whose causal relation is in the highest degree improbable. For instance, the progressive increase in ischaemic heart disease probably correlates closely with the rise in income tax, with the number of telephones in the community, or (inversely) with the decline in knowledge of the classics.

No other field of medical science illustrates so well the fundamental contribution of that academic discipline known as "social medicine," with its technique of the group inquiry, its searching examination of the validity of evidence, and its secure foundation on the mathematically disciplined philosophy of probability. It is right that the clinician should always keep before him the supreme importance of the individual patient, but he must never lose sight of the importance of the patient as a unit in a complex pattern of biological adaptation. The application to diseases in general of the epidemiological techniques which have yielded such a rich harvest in the infectious diseases is the most exciting feature of current medical science.

The implications as regards prevention of such diseases as those we have considered, or of carcinoma of the lung, point to control lying in the hands of the individual rather than in those of the State. The complete control of water-borne infections has been achieved virtually without the knowledge and co-operation of the individual citizen, but anybody who has had experience of training soldiers to practise effective individual antimalarial measures will readily realize how hard it is to secure sustained effective co-operation. When such prophylaxis means avoiding attractive things and practising austere measures the propaganda problems become really formidable. However, the science of propaganda—as we know to our cost—also develops.

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COEXISTENT MYXOEDEMA HEART DISEASE AND PSYCHOSIS

BY

ROWLAND J. CALVERT, Ph.D., M.R.C.P.

ERIC SMITH, D.M., M.R.C.P.

AND

LESLIE G. ANDREWS, M.B., M.R.C.S.

The Medical Unit, Whipps Cross Hospital, London, E.11

The reports of the Committee of the Clinical Society of London (1888) and of Brun and Mott (1913) indicate clearly that an acute psychosis may arise spontaneously in myxoedema. More recent accounts (Stoll, 1932; Zondek and Wolfsohn, 1944; Asher, 1949; Miller, 1952) have focused attention on this fact. Indeed, Asher wrote, "Myxoedema is one of the most important, one of the least known, and one of the most frequently missed causes of organic psychoses." His report evoked editorial comment (*British Medical Journal,* 1949; *J. Amer. med. Ass.,* 1949; *Year Book of Endocrinology,* 1952) and has prompted us to describe two illustrative cases which we have treated in the past six months.

Our patients merited additional clinical and therapeutic interest, as one had associated "myxoedema heart" (Zondek, 1918), while the other had congestive cardiac failure with little cardiac enlargement. The combination of myxoedema heart disease and psychosis has not previously received special attention.

Case 1

A housewife aged 48, who had had previous good health, was admitted on September 15, 1953, with deeply cyanosed lips, orthopnoea, and anasarca. The main myxoedematous features were a creamy complexion with malar flush, dry skin, patchy alopecia of the scalp and outer eyebrows, dry

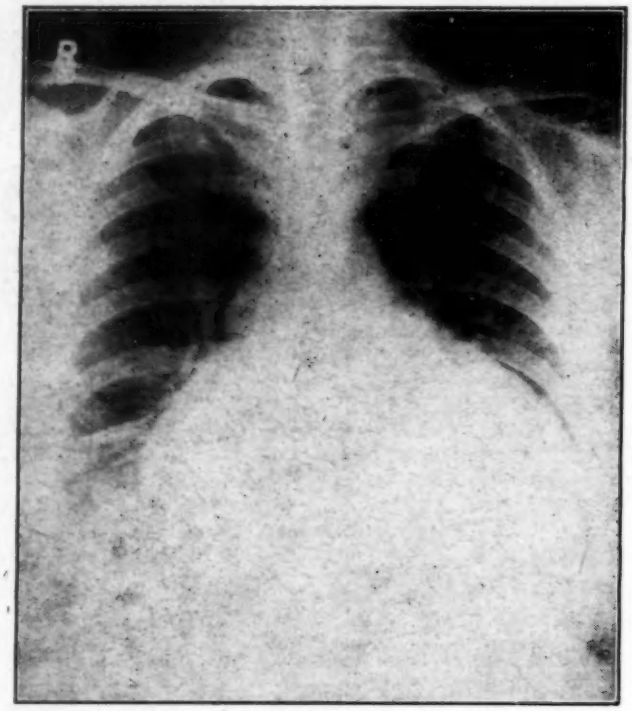

FIG. 1.—Teleradiogram of chest on admission showing classical myxoedema heart.

brittle hair, a deep toneless voice, and slight deafness. The secondary sex characters were normal. She was mentally dull but rational.

The remaining salient physical signs were mainly confined to the cardiovascular system, and included venous congestion, and sacral and ankle oedema. The apex beat could not be located, but on percussion the area of cardiac dullness was increased to the left and right. The cardiac sounds 1 and 2 were muffled but present at all areas and were accompanied by a short apical systolic murmur. The pulse was regular at a rate of 62 a minute, of good volume and without pulsus paradoxus. The radial vessel wall did not feel thickened and there was no locomotor brachialis. The blood pressure was 150/80. Other systems were normal apart from basal crepitations in the chest and a swollen abdomen with a small ascitic effusion and a firm liver edge palpable 3 cm. below the costal margin in the mid-clavicular line.

The immediate teleradiogram (Fig. 1) revealed an enormous cardiac silhouette with sharply stencilled borders and shadowing at the lung bases. The remaining investigations are set out in the Table, where the initial results are compared with those obtained one week before discharge from hospital, when they had reverted towards normal. Neither cardioscopy nor pericardial paracentesis was performed. The urinary neutral 17-ketosteroid excretion was 1.4 mg. a day. The blood Wassermann reaction was negative.

Immediately after the initial tests, treatment was begun with thyroid extract, ¼ gr. (32 mg.) daily. After three weeks on this dose, acute psychotic signs first appeared, while the cardiac silhouette was virtually unchanged. The lung bases were clear and she could now lie flat comfortably. Her mental state warranted urgent certification. She was wildly confused, aggressive, and abusive, with delusions of persecution. Suicidal attempts rapidly followed. They included

Results of Investigations During First Week Compared With Those Obtained Three Months Later

	Early	Late
Thyroid extract daily dose	Nil	8 gr. (0·52 g.) for 2 months
Weight	12 st. 3 lb. (77·6 kg.)	9 st. 4 lb. (59 kg.)
Haemoglobin	79%	82%
B.M.R. (mean value)	−19%	+6%
Serum cholesterol	204 mg. per 100 ml.	152 mg. per 100 ml.
E.C.G.:		
Rate	60/min.	75/min.
QRS voltage	Very low	Normal
Axis deviation	Nil	Left
T waves	Flat or inverted in all leads	Upright. Low voltage in some leads

swallowing smelling-salts, a hair-grip, and buttons torn from her nightdress. She attempted suffocation under her pillows and ruthless self-mutilation by trying to cut her wrists and by violent scratching of her forearms. Next she chewed up the corner of a bed-sheet and tried to swallow it. Further suicidal attempts seemed imminent. Instead of immediate certification we resorted to more vigorous thyroid therapy, realizing that her cardiac state was a relative contra-indication, but predicting a dramatic resultant improvement of her psychosis (Asher, 1949; Miller, 1952). Single daily doses of 1, 2, and 4 gr. (0.06, 0.13, and 0.26 g.) respectively were given for the next three days, aided by persuasion and sedation, without producing cardiovascular distress. Her mania persisted and next day the dose was increased to 8 gr. (0.52 g.) daily. Two days later she was remarkably placid and rational. Further convalescence was uneventful. She continued to take 8 gr. (0.52 g.) of thyroid extract daily without evidence of overdose. Her mental state was normal after one week on this higher dose. She now jokingly referred to her recent bizarre behaviour.

On December 10 she was mentally and physically fit and was discharged home on 8 gr. (0.52 g.) of thyroid extract daily, and keen to resume her household and canteen duties. Her periods had now returned after 10 months' absence. The pulse rate was 80 a minute, the blood pressure 160/95, and the cardiac silhouette was almost within normal limits. The apex beat was easily located in the fifth left interspace just beyond the mid-clavicular line. The cardiac impulse was thrusting in type and the cardiac sounds were pure and of normal intensity. The abdominal signs were unaltered.

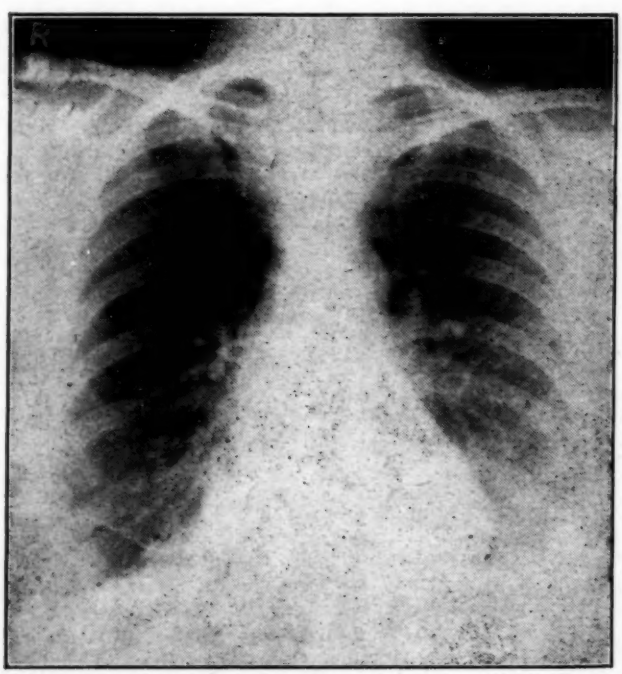

FIG. 2.—Teleradiogram of chest three months after thyroid extract 8 gr. (0.52 g.) daily.

She has since attended the out-patient clinic weekly. On January 16, 1954, her daily dose of thyroid extract was reduced to 6 gr. (0.4 g.) as she complained of palpitations, flushes, excessive perspiration, and insomnia, but not of anginal pain. The pulse rate was 110 a minute, the blood pressure 210/120, and the cardiac silhouette (Fig. 2) remained slightly larger than normal. A fortnight later these symptoms recurred and the daily dose of thyroid extract was further reduced to 4 gr. (0.26 g.), at which level it remained until the time of writing (March, 1954). The pulse remained steady at 70 a minute and the blood pressure at 150/90. Her weight was 9 st. 11 lb. (62.1 kg.); she was symptom-free and able to carry out her duties efficiently. Although slight cardiac enlargement persisted radiologically, there had been no further signs of congestive cardiac failure. She received no digitalis throughout. If the photographic test for myxoedema (Asher, 1949) had been applied before and after a few weeks on thyroid therapy the differences would have been impressive.

Case 2

A housewife aged 58 was admitted to hospital on October 31, 1953, after alternating phases of semicoma and maniacal outbursts during the previous day. She had signs of early congestive cardiac failure and complained of diarrhoea of three years' duration, which was later shown to be the spurious type due to faecal impaction. She was slightly built and diminutive (4 ft. 6 in. (135 cm.) in height and 10 st. 2 lb. (64.4 kg.) in weight) with a microcephalic appearance and a retroussé nose. The myxoedematous features closely resembled those in Case 1. Further examination revealed minimal orthopnoea and venous congestion, moderate ankle and slight sacral oedema, bradycardia (60 a minute) with thickened radial vessel wall and hypotension (115/75), but no other abnormal cardiovascular signs. Apart from the respiratory system, where there were basal crepitations, other systems were normal.

She had never received thyroid medication, and her previous history (from her relatives) revealed that for 17 years she had been subject to manic depressive episodes, two of which had led to prompt mental certification. The various episodes included apathy, mental inaccessibility, fugues, a paranoid state, and assault on nurses. During a previous admission to hospital (July, 1953) for congestive cardiac failure, this disappeared with rest in bed and mersalyl injections but without digitalis medication. During the determination of the basal metabolic rate, however, she became acutely maniacal and suspicious of this procedure, necessitating her third certification before thyroid medication was begun.

On the present admission the possibility of "pituitary myxoedema" was considered in view of her lapses into semicoma, hypotension, and her spare build. This point was never settled, because of her uncooperative state. The determination of urinary excretion of neutral 17-ketosteroids, although of no great differential diagnostic value, had to be deferred because of her frequent urinary incontinence. There was, however, no other supportive evidence of decreased activity of the anterior pituitary gland, as her secondary sex characters were normal, she had a family of five whose ages ranged from 16 to 30, and there was no history of post-partum haemorrhage. She had undoubted arteriosclerosis, but there was no history of a previous coronary thrombosis to explain the hypotension.

The serum cholesterol was 400 mg. per 100 ml. A chest *x*-ray film showed that the cardiac silhouette was not appreciably enlarged. The electrocardiogram showed low voltage with iso-electric or inverted T waves in all leads. The determination of the basal metabolic rate was deferred to avoid a repetition of mania, while it was also appreciated that any result obtained could hardly have been regarded as "basal" so long as there was residual cardiac failure or the possibility of agitation. The Wassermann reaction was negative in the blood, and a similar result had previously been obtained on the cerebrospinal fluid.

Treatment was begun cautiously with ¼ gr. (32 mg.) of thyroid extract daily, and this dose was gradually increased to 3 gr. (0.2 g.) over the next six weeks. We refrained from giving a larger dose in view of the mild psychotic picture, the arteriosclerosis, the congestive cardiac failure, and finally the remote possibility that her myxoedema was of pituitary origin. These latter patients may react unfavourably to even small doses of thyroid extract with adrenal cortical failure (Escamilla, 1950). Digitalis therapy was withheld, as it was not strongly indicated in view of the bradycardia and the mild congestive cardiac failure.

After three weeks' thyroid medication the congestive cardiac failure had entirely disappeared. There was striking improvement in her mental state. This was not expected in view of the long history of psychosis. There were no further attacks of semicoma. Her conversation was now moderately intelligent. She was less suspicious and introverted and more docile, while for the first time in 10 years she read the newspaper. The pulse rate had increased (70 to 80 a minute), but the hypotension remained (110/70). Her weight had fallen to 8 st. 2 lb. (51.7 kg.) and the serum cholesterol level to 124 mg. per 100 ml. The basal metabolic rate had now a mean value of plus 10%. The cardiac size radiologically, and the electrocardiogram, were completely normal. She was discharged on January 21, 1954, feeling fit and free from spurious diarrhoea and urinary incontinence. She has since attended the medical out-patient clinic fortnightly. One month after discharge from hospital her daily dose of thyroid extract was reduced to 2 gr. (0.13 g.), as she was complaining of occasional flushes, but there was no other evidence of thyroid overdosage. She is now able to carry out most of her household duties and shopping. Her attitude to other patients in the ward and to its nursing staff has altered, as she now visits the ward regularly in a friendly fashion after her attendance at the clinic.

Discussion

Our two cases illustrate the dramatic effect of thyroid therapy on both myxoedematous psychosis and myxoedema heart disease. In treating the latter, it is customary to be cautious with thyroid medication (McGavack *et al.*, 1945), using an initial daily dose of about ¼ to ½ gr. (8 to 16 mg.) of the extract, as these patients are especially apt during treatment to lapse into acute congestive cardiac failure or to develop acute coronary insufficiency if larger doses are used. This caution was later waived to some extent in the treatment of our first case when acute psychosis predominated.

It has been shown (Lange, 1944) that capillary permeability is increased in myxoedema. This would explain best the occurrence of a complicating pericardial effusion, which Gordon (1929) first reported. This effusion, however, may not always be a constant, early, and major factor in myxoedema heart (Bell and Beck, 1953), despite the suggestion of Kern *et al.* (1949), for it is also recognized (La Due, 1943) that an additional cause for this massive cardiac silhouette is a dilatation of all the cardiac chambers.

Although myxoedema heart with congestive cardiac failure has been reported, this association is rare (Blumgart and Freedberg, 1952). In our first patient, who was considered to have myxoedema with a pericardial effusion and congestive cardiac failure, the possibility that the anasarca was at least partly due to hepatic cirrhosis and partly to congestive cardiac failure was entertained but not explored. The disappearance, during thyroid therapy, of the oedema but not of the abdominal swelling with its persistent hepatic enlargement and signs of minimal ascites suggests that both aetiological factors were operative. Pure myxoedematous ascites is reabsorbed during thyroid therapy (Paddock, 1950; Tracey and Donovan, 1951; Ferayorni and Sprague, 1952), while the same result occurs in anasarca due to congestive cardiac failure in myxoedema (Fahr, 1928) in which digitalis rarely restores circulatory efficiency (Andrus, 1953). It is also recognized (Hurxthal, 1935; McGavack *et al.*, 1945; Means,

1948) that, as in Case 1, following thyroid therapy in myxoedema heart, the cardiac silhouette may not return to within normal limits for several months.

Concerning myxoedematous psychosis, it is interesting that this appeared spontaneously and for the first time in Case 1 after three weeks on ½ gr. (32 mg.) of thyroid extract daily, thus suggesting the necessity of a larger dose for its control. There have been frequent pleas (Stoll, 1932; Zondek and Wolfsohn, 1944; Asher, 1949; Miller, 1952) for a wider recognition of myxoedema as a cause of acute insanity, especially since failure to recognize it may lead to denial of the one treatment which can be both specific and dramatic. Schwimmer *et al.* (1947), in their review of the clinical manifestations of 40 cases of myxoedema, stressed the fact that the diagnosis is often missed primarily because it is not entertained, while a further important contributory factor is an all too frequent reliance on a complete clinical picture, whereas many of the unmistakable classical signs may be absent. A further drawback, as pointed out by Bartels (1950), is that profound myxoedema may occur in the presence of only a slightly lowered basal metabolic rate or a normal plasma cholesterol value. The latter was demonstrable in our first patient.

There is no constant psychotic picture in myxoedema. Most of these patients have been women. The personality changes cover the wide range of mania, irritable and suspicious character, self-accusation, delusions, hallucinations, melancholia, and a schizoid state, but rarely, as in Case 1, suicidal attempts. At other times there may be lapses into semicoma (Committee of the Clinical Society of London, 1888; Stoll, 1932), as in Case 2. In this transient hibernation it is conceivable, if evidence of vascular disease were found or the myxoedematous signs were less striking, that the cause could be readily misdiagnosed or missed. This cerebral state should not readily be identified with the pre-terminal coma, described by Summers (1953), which no treatment so far has reversed. Concerning the cause of acute myxoedematous psychosis, there has been little study but some speculation.

Mott (1915), however, examined the histological appearances of the brain tissue obtained from the necropsy of such patients. He observed that perinuclear chromatolysis in the cerebral cortex was a constant feature of the few cases studied, but this finding is non-specific. It has also been described in such toxic states as lead encephalitis and alcoholic psychosis, and this led him to suppose that the myxoedematous psychosis was mainly "due to a lack of functional energy which may be correlated with the marked disappearance of the Nissl substance (kinetoplasm), possibly associated with a toxic condition." This would imply that the reduced hormonal influence of the thyroid gland might result in the accumulation of a metabolite which was toxic to the brain. No such substance has so far been identified, and his alternative suggestion of an absence of some substance essential for nerve-cell metabolism merits equal consideration.

Zondek and Wolfsohn (1944), however, attributed the improved mental status after thyroid therapy to "dehydration." They had previously demonstrated that, during thyroid therapy in myxoedema, a diuresis with the mobilization of extracellular fluid results. More recently, the cerebral circulation and metabolism in myxoedema have been investigated by Scheinberg *et al.* (1950), who found that the cerebral blood flow and oxygen and glucose consumptions were all decreased in patients with myxoedema, compared with normal values. Thyroid treatment restored these lowered levels towards normal. These workers suggested that the mental changes in myxoedema were the result of decreased cerebral oxygen and glucose metabolism. They also confirmed the electroencephalographic findings of Bertrand *et al.* (1938) in myxoedema. These include typical low voltage, a lack of alpha waves, and an absence of reaction to a light stimulus, but only one or more of these were regularly present in any one patient. Even, however, if alpha waves are present there is a good correlation of the alpha rate with the metabolic rate in myxoedema (Ross and Schwab, 1939). This test may have occasional value in the confirmation of diagnosis.

Myxoedema may evade diagnosis, may masquerade as other medical or mental disorders, or may fail to be confirmed if reliance is restricted to one test. If myxoedema heart or myxoedematous psychosis or both are present, failure to recognize these or a misdiagnosis means failure to supply the only treatment which is beneficial and at times even dramatic, while without treatment the prognosis is serious. It was believed that in Case 1 a psychiatric disaster was averted and the patient has become a useful citizen, while it is hoped that future certification will be spared in Case 2.

Summary

Two cases of coexistent myxoedematous psychosis and heart disease are described. Both features in both cases responded well to thyroid extract therapy. A brief review and discussion of these two important complications of myxoedema are given. The difficulties in the clinical diagnosis and confirmation of diagnosis are discussed, and the theories on causation of myxoedematous psychosis are briefly mentioned.

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The Anglican Diocese of Nyasaland maintains a number of medical stations situated round the southern half of Lake Nyasa, in Portuguese East Africa, as well as in Nyasaland itself. There are seven small hospitals, two small leprosy settlements, and four other clinics and dispensaries. An annual total of nearly 2,000 in-patients and 35,000 out-patients are dealt with. In 1953 there were over 235,000 out-patient attendances at the medical stations. Most of the hospitals, including that on Likoma Island, are administered by nursing sisters. The headquarters of the medical officer to the Anglican Diocese in Nyasaland is at Malindi. The present medical officer is retiring soon, and the Universities' Mission to Central Africa is endeavouring to find a successor.

REVALUATION OF THE FLOURPAPER TUBERCULIN JELLY TEST

BY

MAXWELL CAPLIN, M.R.C.S., L.R.C.P.
Tuberculosis Officer, London Chest Hospital

JUNE HARRINGTON, M.B., B.S.

C. P. SILVER, B.M., M.R.C.P.
Assistant Tuberculosis Officers, London Chest Hospital

AND

STEFAN GRZYBOWSKI, M.D., M.R.C.P.
Senior Registrar, High Wood Hospital for Children

The tuberculin jelly test is widely used, and with the introduction of B.C.G. its use has been further extended. We in clinic practice, however, have come to distrust the results of the jelly test, and there has been the same dissatisfaction at High Wood Hospital for Children. No fewer than 17 out of 200 children referred there recently for treatment for primary pulmonary tuberculosis proved to be non-tuberculous and tuberculin-negative; the erroneous diagnosis in each of these cases had been based on a jelly test read as positive. We decided, therefore, to carry out an investigation comparing the accuracy of the jelly test with that of the Mantoux.

History

The use of tuberculin jelly was described by Monrad in Denmark in 1936, and the whole early history of the test was first discussed in this country in a leading article in *Tubercle* (1937). Paterson (1944), using a jelly containing 95% old tuberculin (O.T.), considered it equivalent to a Mantoux test of 1:100 dilution. This degree of sensitivity was not generally accepted, and in an effort to increase the sensitivity of the test Deane (1946) tried sandpapering the skin lightly before the application of the jelly. Sandpaper was later replaced by flourpaper (gauge 00 sandpaper). This technique is generally used in children over 5, while for those under 5 the plain jelly is considered quite adequate (Dick, 1950a). Dick (1950b) comparing P.P.D. and O.T. jellies of various strengths, found the 60% O.T. jelly the more reliable. Lendrum (1951) has claimed great accuracy in reading the results, particularly if the test be read as late as the fifth day. In contrast, Coles (1952) and Frew, Davidson, and Reid (1953) have reported a high rate of doubtful and inaccurate results.

One of the major difficulties in reading the test, particularly the flourpaper method, has been that of deciding what skin appearances are essential for a positive result, for each authority has laid down different standards. The main standards that have been advocated are given in Table I.

The present investigation consisted of three parts: (1) a detailed study of a large number of plain and flourpaper jelly tests with simultaneous Mantoux tests; (2) the independent reading of a series of flourpaper jelly tests and of Mantoux tests by a panel of observers who had no special experience of the tuberculin test; and (3) the independent reading of flourpaper jelly tests and of Mantoux tests by a panel of expert observers.

The Jelly Test

Plain and flourpaper jelly tests and Mantoux tests were performed together on 288 children (ages 5 to 15) from two East London schools and from High Wood Hospital for Children. The schools provided a predominantly negative population, and the hospital provided children with active clinical tuberculosis. Of these 288 children, 173 were negative to a 1:100 dilution of O.T., and 115 were positive to 1:100 or higher dilutions of O.T. (Table IV). No fewer than 92 of this latter group were cases of active tuberculosis undergoing treatment in High Wood Hospital. As there is a tendency for active tuberculosis to be associated with high levels of tuberculin sensitivity (Grzybowski, 1951), the Mantoux-positive group showed on the whole a much higher sensitivity than would be the case were it derived wholly from the general population.

The jelly used contained 60% O.T. and was manufactured by Allen and Hanburys. All the jelly tests were applied by one observer in the manner described in the makers' instructions. The interscapular area was cleaned with acetone, and control jelly was squeezed out in a horizontal line about ½ in. (2 cm.) long to the left of the spine. Below the control, tuberculin jelly was applied in the form of a V, the arms of which were also about ½ in. (2 cm.) long. On the right side of the spine the whole area was lightly sandpapered by six strokes with No. 00 sandpaper (flourpaper), and the control and the tuberculin jelly were applied in the same way. Zinc oxide strapping was placed directly over the jelly, and removed on the third day. The reaction was examined on the third, fourth, and fifth days and recorded in a standard manner, the results being read together by at least three of us. In each test the presence of erythema and of oedema (induration, raising) was recorded; these features concerned the base of the lesion. The elevations upon the base were recorded as papules, vesicles, vesicopapules, and pustules. Staining, crusts, and scratch marks were also noted.

The Mantoux Test

The tuberculin dilutions were freshly prepared from old tuberculin (B.W. Batch No. T.2732.S), and separate syringes and needles were used for each dilution. To determine the degree of tuberculin sensitivity the following procedure was adopted. In the predominantly negative population of the schools an intradermal injection of 0.1 ml. of 1:1,000 dilution (10 T.U.) was given on the first day at the time of the jelly testing. The result was read on the third day (48 hours); if negative, the test was repeated with 1:100 dilution (100 T.U.); if positive, with both 1:10,000 and 1:100,000 dilutions (1 T.U. and 0.1 T.U. respectively). The

TABLE I.—*Varying Standards for Judging a Positive Jelly Reaction*

Author	Method	Time of Reading Recommended	Standard for *Positive Result	Remarks
Paterson (1944)	Plain jelly	48 hours and several days thereafter	Erythema or slight vesiculation in shape of marking used	Negative result showed a completely normal skin
Clark (1951)	„ „	72 or 96 hours	Definite erythema with at least two vesicles; erythematous area often palpably indurated	
Deane (1946)	Sandpaper jelly	96 hours	None	No. 0 sandpaper used. All later observers have used No. 00
National Tuberculin Survey 1949–50 (M.R.C., 1952)	Flourpaper jelly	72 to 96 hours	Raised erythema with or without vesiculation; coalescence of vesicles to form V- or heart-shaped area of induration might occur	
Dick (1950b)	„ „	72 to 96 „	Vesiculation. Coalescence of vesicles to form V- or heart-shaped area of induration might occur	Fewer than four vesicles should be considered a doubtful reaction. Erythema should be ignored
Lendrum (1951)	„ „	96 hours	Six or more papules in shape of original application	
Makers' instructions (Allen & Hanburys)	Plain or flourpaper jelly	72 hours and thereafter up to one week	Slightly vesicular mark	Erythema should be ignored

results were read on the fifth day (48 hours later). The children from High Wood were tested with 1:10,000 and 1:100,000 dilutions (1 T.U. and 0.1 T.U. respectively) on the first day, and the results were read on the third day (48 hours). Only one High Wood child was negative to the 1:10,000 dilution (1 T.U.) and he was retested with the 1:1,000 dilution (10 T.U.) and shown to be positive.

A reaction two to four days after injection, with not less than 5 mm. diameter of oedema with surrounding erythema, was regarded as a positive Mantoux result.

Development of the Skin Lesion

The development of the plain jelly lesion can be used to explain that of the more complicated flourpaper reaction. In the Mantoux-positive group, if the reaction to the plain jelly was severe, the area covered by the jelly was raised, reddened, and oedematous. This oedema was most pronounced at 72 hours. Vesicles were appearing at 48 hours, but tended to be small, increasing in size and number by 96 hours. Papules were much less common, and tended to be more numerous initially. Pustules were rare; crusts were never seen. When the reaction was less severe there were separate islands of reddening and oedema, often surmounted by one or more vesicles. The incidence of each type of skin change is given in Table II, which shows that

TABLE II.—*Percentage Distribution and Type of Plain Jelly Lesion According to Mantoux State* (1:100)

Reaction	Mantoux-positive Group 115 Children			Mantoux-negative Group 173 Children		
	Hours			Hours		
	48	72	96	48	72	96
Erythema ..	63	69	72	1	—	—
Oedema ..	27	48	48	—	—	—
Staining ..	3	—	9	—	—	—
Vesicles ..	56	66	77	—	—	—
Vesicopapules	17	10	3	1	—	—
Papules ..	14	7	3	1	—	—
Pustules ..	1	3	1	—	—	—
Crusts ..	—	—	—	—	—	—
Scratch marks	—	—	—	—	—	—

a reaction of one type or another occurred in the majority of the Mantoux-positive children, while there was no reaction at all in the Mantoux-negative group at 72 and 96 hours. There is little doubt that this high degree of correlation in our Mantoux-positive group is due to the high levels of sensitivity in this group; with the lower levels of sensitivity encountered in the general population more cases would show a negative reaction. It is for this reason that the use of flourpaper was originally introduced.

When the flourpaper technique was used the reactions in the Mantoux-positive group were more violent than those seen with the plain jelly. At 48 hours there was intense erythema and oedema, with pustules rather than vesicles. By 72 hours the whole reaction was more pleomorphic than that of the plain jelly. The surface was oozing serum, and many vesicles and pustules had burst. At 96 hours the process had gone further, and often the base was flat though covered by dried or drying vesicles or by crust. If the jelly response was less marked the reaction was patchy, and in many cases was hard to differentiate from

TABLE III.—*Percentage Distribution and Type of Flourpaper Jelly Lesion According to Mantoux State* (1:100)

Reaction	Mantoux-positive Group 115 Children			Mantoux-negative Group 173 Children		
	Hours			Hours		
	48	72	96	48	72	96
Erythema ..	95	90	84	68	34	11
Oedema ..	79	69	41	9	2	—
Staining ..	—	1	10	1	4	25
Vesicles ..	22	31	24	11	1	—
Vesicopapules	6	5	4	11	—	—
Papules ..	3	3	1	13	9	1
Pustules ..	70	30	4	48	2	—
Crusts ..	5	57	63	12	25	39
Scratch marks	31	27	31	41	53	54

that seen in the Mantoux-negative cases. Despite careful use of the flourpaper the majority (all but 28) of the 173 Mantoux-negative children showed some reaction at some time (see Table III). In these Mantoux-negative children a reaction elicited by the control jelly was much less often seen and was always less severe than the reaction due to tuberculin jelly, though one would have expected them to be the same. We are unable to account for this surprising finding, as the only apparent difference between tuberculin and control jelly is that of tuberculin content. It may be that the position in which the two jellies are placed in relation to the force and direction of the stroke of the flourpaper may provide a clue. The fact remains, however, that in this series the control jelly was of no value.

If Tables II and III are compared it is apparent that, whilst the plain jelly lesion is relatively simple, the flourpaper lesion is a very complex one. The frequency of pustules at 48 hours and the commonness of crusting and scratch reactions in both positive and negative reactors form a sharp contrast with the plain jelly reaction. All the lesions lying in the Mantoux-negative half of Table III can only be due to the use of flourpaper.

Various Standards Applied to the Skin Lesion

Our findings may be compared with the standards laid down by different authorities. Two commonly accepted standards have been chosen, and are named Standard A and Standard B.

Standard A.—A positive reaction: an area of raised erythema (erythema and oedema) with or without vesiculation. A negative reaction: any reaction other than this.

This was the standard accepted by the Medical Research Council (1952) in the National Survey 1949–50.

Standard B.—A positive reaction: at 72 hours four or more skin elements—that is, vesicles, vesicopapules, papules, and pustules—and at 96 hours six or more skin elements; or an area of raised erythema at either 72 or 96 hours considered to be due to coalescence of vesicles. (The substitution of six elements at 96 hours for four at 72 hours affected only three cases.) This standard is similar to the standards laid down by Dick (four or more vesicles) and Lendrum (six or more papules) (see Table I). There seems little doubt that the vesicles of Dick are the papules of Lendrum.

Table IV shows the results when Standard A and Standard B are read at 72 and 96 hours.

TABLE IV.—*Flourpaper Jelly Results. Comparison with Mantoux Sensitivity*

Mantoux Sensitivity	No. of Children	72 Hours		96 Hours	
		Positive to Standard A	Positive to Standard B	Positive to Standard A	Positive to Standard B
1:100,000 +	64	47 (73%)	62 (97%)	27 (42%)	38 (59%)
1:10,000 +	39	27 (69%)	32 (82%)	13 (33%)	20 (51%)
1:1,000 +	7	2 (29%)	3 (43%)	2 (29%)	3 (43%)
1:100 +	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positive ..	115	76 (66%)	97 (84%)	42 (37%)	61 (53%)
Negative ..	173	0 (0%)	18 (10%)	0 (0%)	0 (0%)

As might be expected, the proportion of children showing a positive reaction to the jelly is closely related to the level of tuberculin sensitivity. But even in those showing a high sensitivity the jelly test was sometimes negative. Thus it does not appear permissible to state that the jelly test is equivalent to a particular dilution of tuberculin. In considering Table IV it must be remembered that this group of Mantoux-positive children is selected. Were these children a representative sample of the population the level of sensitivity would be lower and the discrepancy between Mantoux and jelly tests among the tuberculin-positive children would be greater.

Table IV shows that by applying these two standards at 72 hours there will be a considerable error in reading the test; using Standard A, 34% of tuberculin-positive children will show a negative reaction, but there will be no false-positive reactions among the tuberculin-negative children.

The introduction of Standard B will diminish the number of false-negative reactions to about 16%, but will lead to the occurrence of about 10% of false-positive readings. At 96 hours, using either standard, the number of false positives falls to zero, but the number of true positives also falls—that is, the false negatives increase to 63% according to Standard A and 47% according to Standard B. Applying other standards, none was found to give satisfactory results. It was easy to shift the body of the readings from negative to positive or from positive to negative by accepting or rejecting some particular factor.

The Non-expert Panels

Is the flourpaper jelly test as easy to read as its advocates maintain? This part of the investigation was designed to answer this question by showing what accuracy and correlation could be achieved by relatively inexperienced observers.

It was arranged that at one of the schools a panel of four doctors should read the flourpaper results and the Mantoux results on the fourth day (72 hours), and another panel of similar constitution should read both tests on the fifth day (96 hours). Each panel consisted of three general practitioners and one paediatric registrar. Each doctor was provided with the makers' instructions for reading the flourpaper jelly test and also instructions for reading the Mantoux test. They read the tests independently, recording their findings as positive, negative, or doubtful. All the flourpaper jelly tests were read first, only the children's backs being exposed, and then all the Mantoux tests, only the left forearm being exposed. Of the 108 children examined, 101 were negative to a 1:100 dilution of O.T., and 7 were Mantoux positive.

Table V shows that there was little disagreement between the four doctors of each panel when reading the Mantoux test, but their disagreement over the jelly readings was very considerable. Unanimous agreement was reached in less than a third of the jelly readings. If three agreements are accepted as a satisfactory degree of correlation, 68% agreement is all that was achieved by the more consistent panel—that is, the 96-hour panel—compared with 98% agreement by the same panel when reading the Mantoux test.

TABLE V.—*Percentage Agreement Between Non-expert Observers*

	Reading at 72 Hours		Reading at 96 Hours	
	Jelly	Mantoux	Jelly	Mantoux
Unanimous agreement ..	31%	78%	26%	96%
3 out of 4 doctors agree ..	34%	18%	42%	2%
Less than 3 agreements ..	35%	4%	32%	2%

Turning now to the individual readings of each observer, Table VI gives their performance related to the Mantoux state as determined by us.

TABLE VI.—*Non-expert Panels. Individual Performance of Each Observer Compared with the Mantoux State* (1:100)

	101 Mantoux-negative Children								7 Mantoux-positive Children							
	Jelly Reading at															
	72 Hours				96 Hours				72 Hours				96 Hours			
Observer:	A	B	C	D	E	F	G	H	A	B	C	D	E	F	G	H
True readings	85	75	56	40	35	72	84	39	5	5	4	1	6	1	6	6
False "	8	6	34	33	63	26	0	60	1	2	3	0	1	1	1	1
Readings recorded as doubtful	8	20	11	28	3	3	17	2	1	0	0	6	0	5	0	0

Only three out of the eight observers from both panels secured a fair correlation between their jelly readings and the Mantoux state. Both registrars (Dr. A and Dr. G), if their doubtfuls be disregarded, secured some impression of the tuberculin state, but even the more accurate of the two recorded as many as 17 doubtfuls and the less accurate 8 false positives. One practitioner (Dr. B) approached their performance, but the remaining practitioners showed remarkable variations in their readings, two reading 60 or more false positives and one being in doubt on 34 occasions. The lack of correlation shown in Table V is not, therefore, a matter of one observer disagreeing with all the others, but is due to the variety of opinions expressed about each result.

In contrast, reading the Mantoux tests the panels achieved good agreement, not only among themselves but also with our readings. Three out of the eight completely agreed with our readings, and three disagreed only twice; the largest number of times any observer disagreed was 21 times, but he recorded 20 results as doubtful.

The Expert Panels

This part of the investigation was designed to answer two important questions: (1) Could two experts in the use of the flourpaper jelly test obtain a high degree of correlation between their readings? (2) What correlation is there between the flourpaper jelly test and the Mantoux test when these tests are done at the same time, on the same individual, the tests being performed and read by doctors experienced in each?

To undertake this investigation we enlisted the aid of a chest physician who had written favourably about the flourpaper test. She asked a colleague with similar experience to join her in forming the "jelly panel." Two of us acted as the "Mantoux panel."

The school chosen for the investigation was a girls' grammar school in East London with 450 pupils, whose ages ranged from 10 to 17: 437 of the girls took part in the investigation.

Each girl had a flourpaper jelly test applied by one member of the jelly panel, and received a Mantoux test (1:1,000) given by one member of the Mantoux panel.

On the third day (48 hours later) the Mantoux tests were read independently by the two doctors of the Mantoux panel. They were seated at opposite sides of the examination room and were separated by a screen. The pupils filed past each in turn, exposing only the left forearm, and the results were recorded on specially prepared lists. These lists, when completed, were handed to the schoolmistress in charge of the arrangements; she checked the correlation at the end of the session.

On the fifth day (96 hours) the jelly panel, taking the same precautions, read their jelly tests. This time the pupils' forearms were covered and only the backs were exposed.

Table VII illustrates the correlation between the Mantoux observers and that between the jelly observers.

TABLE VII.—*Showing Correlation Between Mantoux Observers and Between Jelly Observers*

No. of Children Tested	Correlation between Mantoux Observers		Correlation between Jelly Observers	
	Agreement	Disagreement	Agreement	Disagreement
437	436 (99·8%)	1 (0·2%)	277 (63·4%)	160 (36·6%)

It will be seen that the Mantoux panel secured 99.8% agreement, whereas the jelly panel secured only 63.4% agreement.

The correlation between each jelly observer and the Mantoux state (1:1,000) can now be considered. Of the 437 children tested the Mantoux results of two were omitted; in one, both Mantoux observers recorded their only doubtful result; in the other, the Mantoux observers recorded their only disagreement. The remainder consisted of 435 children whose Mantoux state had been determined and agreed upon. The performance of each member of the jelly panel was then compared with this Mantoux state.

Table VIII illustrates the poor correlation that was obtained. Dr. X recorded no fewer than 123 (34%) of the Mantoux-negative children as positive, and was in doubt

Table VIII.—*Showing Correlation Between Each Jelly Observer and the Mantoux State* (1:1,000)

Mantoux State (1:1,000 O.T.)	Jelly Observer Dr. X			Jelly Observer Dr. Y		
	Positive	Negative	Doubtful	Positive	Negative	Doubtful
74 positive children	68	4	2	61	11	2
361 negative children	123	185	53	32	325	4

on 55 occasions; however, she recorded only four (5%) false-negative readings. Dr. Y gave 32 (9%) false-positive readings, but 11 (15%) of the Mantoux-positive children were recorded as negative. Subsequently Dr. X, the observer who had applied the jelly tests, attributed the unsatisfactory results to hurried application of the tests and over-scarification of the skin. Both Mantoux and jelly tests were completed in just over three hours, as the working conditions were excellent and no delays occurred. In our opinion hurried application could not account for the discrepancy between the readings of the two jelly observers.

Discussion

The first part of this investigation traced the development of the skin reactions resulting from the plain and the flourpaper jelly tests applied in the same individual simultaneously. It illustrated the range and type of the lesions produced, and it enabled us to correlate the findings with the standards laid down by various authorities. Simultaneous Mantoux tests with graded dilutions of O.T. allowed the comparison between the two tests at various grades of sensitivity. Our findings showed that the flourpaper jelly produced a complex reaction consisting of numerous elements of which none was specific to the Mantoux-positive members of our series. No single factor or group of factors could be obtained which would coincide with the Mantoux findings. Whichever standard was employed produced its quota of false positives or false negatives or both, and any attempt to reduce the one increased the other. Nor was control jelly of any real value in distinguishing the false from the true reaction.

The second part of the investigation illustrated the widely differing results obtained when the flourpaper jelly test is read by those without special experience of the test. The non-expert panel were unanimously agreed on their findings in fewer than one-third of the tests at 72 hours, and at 96 hours another panel achieved unanimous agreement in only one-quarter.

The third part of the investigation demonstrated clearly that the jelly test, even in expert hands, cannot be read accurately. The jelly panel, consisting of two experts reading the test which one of them had performed, disagreed 160 times out of 437 (37%). This is a serious lack of agreement. It is obvious that in expert hands an unsatisfactory correlation can only mean an unsatisfactory test.

These results show that the flourpaper jelly test is not accurate enough for testing either contacts or those suspected of tuberculosis. A false-positive reading is common and will result in a child contact not receiving B.C.G. vaccination. Again, if such a child develops some minor pulmonary infection associated with radiological changes the mistaken diagnosis of tuberculosis may be made. A false-negative result also carries its hazards, for in many clinics and hospitals such a result is not always followed by an intradermal Mantoux test, and the child may not be considered to require a chest *x*-ray examination in the absence of symptoms. A case of tuberculosis may thus remain undiagnosed.

The use of the jelly test in surveys also has little to commend it. It is obvious that, for accurate results to be obtained, the standard of a positive reaction must be strict in order not to allow any false-positive readings among the tuberculin-negative children. In such circumstances many tuberculin-positive children will be missed, and it is therefore essential to perform an intradermal test subsequently. When only a minority of the children in a community have been infected with tuberculosis, as is the case in this country, then in any group of children under survey the proportion found to be tuberculin-positive through the jelly test will be small. In other words, the sensitivity of the jelly test when read according to rigid standards to avoid the false-positive error is too low to make it a satisfactory screening test, because the great majority will, anyway, require a subsequent Mantoux test.

Certain surveys have been carried out with the jelly test alone, without subsequent Mantoux tests. If the standards of the positive result were similar to those applied by the observers in the second and third parts of this investigation, both false-positive and false-negative readings would be obtained. They would tend to cancel each other to a varying degree, depending on the standards adopted and on the proportion of tuberculin-positive children in the population. In certain circumstances the end-result of such investigations could give a reasonable figure for the tuberculin state of the population concerned, but this is obviously an unsatisfactory way of conducting a tuberculin survey.

Tuberculin jelly is cheap and stable, it can be easily applied, and it possesses the great advantage of being painless, but all these virtues are of no account if the test cannot be read accurately. The inaccuracy of the flourpaper jelly test readings in both expert and non-expert hands precludes its use both in clinic practice and in tuberculin surveys.

Summary

Plain and flourpaper jelly tests were performed on 288 children aged 5 to 15 whose tuberculin sensitivity had been determined by Mantoux tests with graded dilutions of O.T. The jelly lesions were examined on three successive days. The flourpaper test findings were compared with various standards advocated for judging positive and negative results. Whichever standard was used produced false results.

Non-expert observers independently reading the flourpaper tests of 108 of these children at 72 and 96 hours did not agree among themselves or with the Mantoux state. They agreed well over their Mantoux results.

Flourpaper jelly and Mantoux tests (1:1,000) were performed simultaneously on 437 girls aged 10 to 17. Two expert observers reading the jelly tests independently disagreed 160 times. Two other observers reading the Mantoux tests independently disagreed only once.

It is concluded that the flourpaper jelly test is unsatisfactory both in clinical practice and in tuberculin surveys.

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ENDOCARDIAL FIBROSIS IN THE SUDAN

BY

W. O'BRIEN, M.D., M.R.C.P.

From the Kitchener School of Medicine, Khartoum, Sudan

Bedford and Konstam (1946) and Davies (1948) described series of cases of heart failure in Africans in which the chief feature at necropsy was endocardial fibrosis. Gillanders's (1951) cases among the Bantus appear to be different. Coming to the Sudan in 1952, I was struck by the number of working-class patients with congestive heart failure in which none of the classical causes of heart failure could be implicated but which corresponded closely to the clinical descriptions of endocardial fibrosis. These patients were for the most part Arabs and not Negroes. Unfortunately it was exceedingly difficult to obtain permission for post-mortem examination. Finally, we obtained permission for two necropsies, and both confirmed the condition of endocardial fibrosis. The following is a clinical description of the condition in 25 patients. In this class of patient rheumatic heart disease and hypertension are common, and yet these cases of endocardial fibrosis with failure outnumbered the total of all other types of heart failure seen by me.

The patients came from all over the Sudan. There were seven peasant farmers, four labourers, four servants (including three cooks), three porters, a cart-driver, a mechanic, a tailor, a shepherd, and three women. Their ages varied from 35 to 80 years, with the major incidence in the fifth decade. Their average age was 54 years.

The diet of each case was carefully recorded, and in only two was it obviously deficient. The only previous illnesses of note were malaria in six cases, syphilis in two, bilharziasis in one, and possibly rheumatic fever in one.

The duration of symptoms varied, but in 18 out of the 25 cases it was under six months. The symptoms started with breathlessness, usually on exertion, but sometimes first noticed on lying down at night. This nocturnal dyspnoea was severe and prevented sleep. Four patients started with pulmonary infarctions. Anginal pain was absent in all cases but one in spite of careful inquiry about such pain. After a variable time there followed swelling of the legs and abdominal distension and discomfort, with or without vomiting.

On examination the patients were of good physique. The pulse was rapid and usually regular, though in five cases there were numerous extrasystoles and in three there was auricular fibrillation. The pulse was of small volume in half the cases and of normal volume in the others. The blood pressure was normal and not particularly low. The jugular venous pressure tended to be very high, and in 10 cases the marked systolic pulsation seen in tricuspid incompetence was present. The liver was usually very large and in three cases was pulsating. Ascites was found in seven patients and oedema of the legs in all.

The apex beat was displaced into the axilla but varied in character, sometimes being difficult to feel and sometimes heaving. The intensity of the heart sounds also varied, but a triple rhythm from addition of the third heart sound was usual. A presystolic triple rhythm was heard in two cases. Nearly every case had a systolic murmur at the apex, the intensity varying between grades 2 and 4.

General cardiac enlargement with pulmonary congestion was confirmed by radiography. Undue enlargement of the left auricle was not found. The electrocardiographic changes were those of widespread myocardial damage. Right bundle-branch block was present in four, left bundle-branch block in three, inversion of the T wave in standard lead I and in chest leads V_{4-7} in seven patients, and inversion of the T wave in lead I and V_4 in one patient, whilst in two the T wave was inverted in all leads. The haemoglobin was normal in all cases but one. Liver biopsy and histological examination in 11 cases merely showed the changes of passive congestion.

All but five patients were treated with rapid digitalization and mersalyl. Following Gillanders's experience, five cases were given rest only and a full diet, but in all five rapid deterioration necessitated the use of the above drugs. Seven patients died in hospital either in severe heart failure or in sudden peripheral circulatory failure. One patient died after several months in hospital with acute miliary tuberculosis and another from a lung abscess, both conditions having been acquired in the wards. Two patients discharged themselves after treatment had failed to improve their condition; 16 out of 25 patients left the hospital free from congestive failure.

In the following illustrative cases the words "marrissa" and "kisra" recur. Kisra is a sort of pancake made from sorghum, while marrissa is a drink of varying alcoholic content brewed from sorghum grain and said to be particularly rich in vitamin B_1.

Case 1

A labourer aged 45, living in Singa, became ill four months before admission, a number of symptoms appearing at the same time. He became jaundiced, with dark urine and loose green stools, upper abdominal pain, breathlessness particularly at night, abdominal distension, and swelling of the legs. He also developed a cough, which became worse just before his admission, when he began to cough blood-stained sputum. During this illness he had irregular fever. He had never had rheumatic fever, syphilis, or bilharziasis, but had had malaria. His diet was full, consisting of meat five times a week, milk with tea, two eggs a day, fresh vegetables, and kisra. He drank no alcohol.

Examination.—He was of normal build; his pulse was 84 a minute, irregular with extrasystoles, and of small volume; B.P. 100/80; the thyroid was normal and there were no signs of thyrotoxicosis; jugular venous pressure was very high, with marked systolic pulsation; rales were heard at both bases; the liver was enlarged nearly to the umbilicus; ascites and oedema of the legs were present. The apex beat was displaced outwards; the heart sounds were normal apart from a loud third heart sound heard in the apical and tricuspid areas and a widely split second sound in the pulmonary area. A systolic murmur (grade 3) was heard at the apex. *X*-ray examination showed general cardiac enlargement with an opacity at the right lung base. E.C.G. showed right bundle-branch block. He was treated with digitalis and mersalyl but died after three days.

At necropsy the abdomen was full of straw-coloured fluid and the liver was large and cirrhotic. The lungs were oedematous, and there were several small infarcts and a large one at the right base. The ventricular walls were both hypertrophied and dilated, and a white sheet of fibrous tissue spread from the apex up the ventricular walls, over the papillary muscles, involving the tricuspid valve, which

was very dilated (the whole hand could be passed through). The right auricular appendage was full of ante-mortem clot. All the other valves and the coronary arteries were normal.

Case 2

A camel shepherd aged 40, from Gatana on the White Nile, had been perfectly well until six weeks before admission, when he noticed slight pain in his knees, ankles, and wrists; with this was a slight fever. These symptoms lasted just over a week and then cleared. Three weeks before admission he developed abdominal distension, and ten days later breathlessness on exertion and on lying down. Three days after this his ankles swelled. He had never had rheumatism or syphilis. His diet was probably deficient. He shared 1¼ lb. (570 g.) of meat once a month with his family of six. Their camel milk was skimmed to sell the cream. The remainder of the diet consisted of vegetables and kisra. He drank some marrissa once a month.

Examination.—He was a tall spare man; his pulse was 150 a minute, of small volume, and regular; B.P. 110/85; the jugular venous pressure was very high; rales were heard at both bases; the liver was enlarged; ascites and oedema of both legs were present. The apex beat was displaced outwards and was tapping. The heart sounds were normal apart from a third heart sound, and a systolic murmur (grade 3) was heard at the apex. The Kahn test was negative; haemoglobin 15 g.%; W.B.C., 4,400, with 8% eosinophils. A week later eosinophils amounted to 18% in approximately the same total count. E.C.G. showed left axis deviation with a biphasic T wave in lead I, and inverted T in lead 6 and biphasic T in V_7. He improved slightly on digitalis and mersalyl, but died suddenly six weeks later after an attack of peripheral circulatory failure.

At necropsy the liver was large and showed the typical nutmeg appearance of passive congestion. The peritoneum was full of fluid. The lungs were oedematous and contained small infarcts. Both ventricles were grossly dilated, the walls being extremely thin. The heart muscle was pale, uniform, and not scarred. The valves except the tricuspid were normal, the latter being dilated and obviously incompetent. On the endocardium were numerous pale firm areas, and the apex of the right ventricle was full of ante-mortem clot. The coronary arteries were normal.

Case 3

A peasant from Merawi aged 55 was a fit man three months before admission, performing the very heavy work entailed in cultivating land which has to be irrigated and worked by hand. He then began to notice increasing breathlessness on exertion, a dry cough, and palpitation. He also had attacks of breathlessness and had to sleep propped up. Two months later his ankles swelled and he developed upper abdominal pain and distension. Previous to this he had had no illness of note. His diet consisted of 1 lb. (450 g.) of meat every four or five days, milk, vegetables, dates, and kisra. He took no alcohol.

Examination.—He was well built; his pulse was 120 a minute, regular, and of normal volume; B.P. 120/90; the thyroid was normal and there were no signs of thyrotoxicosis; the jugular venous pressure was high; the liver was enlarged and tender; and oedema of the legs was present. The apex beat was in the mid-axillary line, the heart sounds were normal except for a loud third heart sound heard in the apical and tricuspid areas. A systolic murmur (grade 3) was heard at the apex. *X*-ray examination confirmed general cardiac enlargement. The haemoglobin was 91%. E.C.G. showed left bundle-branch block. Liver section and histological examination were normal.

Two days after admission he suddenly lost consciousness, and when he awoke two hours later he had a left hemiplegia, which in turn passed off in 48 hours.

Treatment with digitalis and mersalyl rapidly cleared the venous congestion. He was discharged with a very large heart and a loud third heart sound, but free from failure.

Case 4

A labourer from Merawi aged 48 became breathless on exertion a year before admission. A month before admission he became very breathless in bed and two weeks later his ankles swelled. He had had frequent attacks of malaria in the past but no other illnesses of note. His diet was full, consisting of daily meat, vegetables, milk, and kisra. He had never taken much alcohol and had abstained altogether for five years.

Examination.—He was a tubby little man; his pulse was 140 a minute and regular; B.P. 135/90; the thyroid was normal and there were no signs of thyrotoxicosis; the jugular venous pressure was very high; the liver was enlarged to the umbilicus. The apex beat was felt in the mid-axillary line and was thrusting. The heart sounds were normal except that the second sound in the pulmonary area was widely split. A systolic murmur was heard in the apical and tricuspid areas. *X*-ray examination showed considerable general cardiac enlargement. The haemoglobin was 101%. E.C.G. showed right bundle-branch block, and liver section revealed only the changes of passive congestion. The Kahn test was negative.

The patient responded well to digitalis and mersalyl, and was discharged free from heart failure.

Case 5

A 35-year-old mechanic from Khartoum developed left pleuritic pain with a dry cough fifteen years before admission. He began to cough up blood, and a week later woke up in the night severely breathless. Three days later his legs swelled and he noticed epigastric pain. He had never had any previous illness of note. His diet was full, with meat daily, and he lived in a well-to-do household.

Examination.—He was of good physique, but in severe congestive heart failure. His B.P. was 120/80; the apex beat was felt in the anterior axillary line, and the heart sounds were normal apart from a presystolic triple rhythm best heard in the tricuspid area. *X*-ray examination of the chest showed general cardiac enlargement with an opacity in the left mid-zone. The Kahn test was negative; haemoglobin 100%; no eosinophils seen in a count of 8,000 white cells. E.C.G. showed an S wave in lead I, with a diphasic T wave and an inverted T wave in leads II and III. The T waves were also inverted in V_6 and V_7. The S wave in V_1 was markedly notched.

The patient responded well to digitalis and mersalyl, and was discharged a month later free from heart failure.

Case 6

A 65-year-old ex-labourer from Khartoum one year previously suddenly became very breathless on exertion and on lying down. There was swelling of his ankles. He was admitted to hospital and found to be in congestive heart failure. Digitalis and mersalyl were given and he was discharged two months later free from heart failure. In three weeks' time he was readmitted, again in congestive heart failure. This time he had auricular fibrillation and the E.C.G. showed the presence of right bundle-branch block. Once again he responded to the same treatment and was discharged free from heart failure. He remained well for nine months, but after this his breathlessness returned and he was unable to sleep at night. He had had syphilis when 20 years of age but no other illnesses of note. His diet was adequate, with meat, milk, eggs, and fresh vegetables daily in addition to kisra.

Examination.—He was a tall gaunt man who was breathless in bed. His pulse was 50 a minute (he had been on digitalis), irregular from auricular fibrillation; B.P. 145/85 approximately; the jugular venous pressure was very high; the liver was enlarged to the umbilicus and tender; rales were heard at both bases; ascites and oedema of the legs were present. The apex beat was felt between the anterior and mid-axillary lines and was heaving. The second sound

in the pulmonary area was split and there was a systolic murmur (grade 3) at the apex. The Kahn test was negative. *X*-ray examination showed general cardiac enlargement with no particular enlargement of the left auricle. The liver section showed the changes of passive congestion only. E.C.G. showed auricular fibrillation and right bundle-branch block.

Once again he responded to digitalis and mersalyl, and was discharged free from heart failure.

Case 7

A 42-year-old cook from El Obeid drank a huge quantity of water one evening during Ramadan, when the Muslim takes no fluid from sunrise to sunset. Following this he felt exhausted and generally unwell. Next morning he woke with rapid palpitation of the heart, and this continued on and off for four days. He was admitted to hospital, and after an E.C.G. had been done a diagnosis of paroxysmal ventricular tachycardia was made and the rhythm was restored to normal by quinidine. He was discharged and remained well for five months, when, a month before the present admission, he had a return of the palpitation. There was no breathlessness, but he complained of abdominal distension during the attacks of palpitation.

Examination.—His pulse was 110 a minute, irregular from extrasystoles, and of small volume; the thyroid was normal and there were no signs of thyrotoxicosis; B.P. 130/100; the jugular venous pressure was very high. The apex beat was displaced outwards and the heart sounds were normal apart from a third heart sound heard at the apex and a systolic murmur (grade 3) heard in the same place. E.C.G. showed inversion of the T waves in leads I, V_2, and V_4, with a biphasic T wave in V_6. *X*-ray examination of the chest confirmed general cardiac enlargement, and liver section showed the changes of passive congestion. He remained in hospital for two weeks without any prolonged attack of palpitation; the pulse rate then rose to 180 a minute and he became very breathless. His hands were cold and he was disorientated. Two days later the pulse rate fell to 48, and then after a few hours he collapsed and died.

Discussion

The aetiology of the condition remains unknown. This series of cases does suggest, however, that certain of the tentative theories put forward previously will not do. Coronary artery disease, at least of the main arteries, is not a factor: the site of the lesion is against it. Anginal pain was strongly denied and atheroma is rare in the Sudanese working-class. During 18 months I have heard only one patient complain of anginal pain, and he had syphilitic aortic incompetence. This is in strong contrast to the middle and wealthier classes of patients, in whom cardiac infarction is common, often at an early age.

Undernutrition and malnutrition were not present in these patients. The Sudan has been prosperous for some time now, and the protein content, including meat protein, is at least adequate. Young children sometimes show nutritional deficiencies and kwashiorkor occurs, but the absence of chronic liver damage in these cases is against any long period of malnutrition. The disease was found in three cooks. Moreover, Gray (1951) reported the disease in a British Colonial Service doctor and a District Magistrate from Nigeria. Edge (1946) also described what must have been a similar case in a European from West Africa. Alcohol does not appear to have been a factor in these cases.

The disease is not limited to any race and is common in those of Arab stock. Syphilis was not a factor. The uneducated Sudanese is never afraid to admit a history of this condition, and, moreover, the Kahn test was negative in all the cases in which it was done. Eosinophilia was found in only two patients, suggesting that the high incidence in other series is due to parasitic infestation rather than being a mark of the allergic nature of the condition. Again advanced liver disease was found in only one case.

Heart failure due to pulmonary bilharziasis occurs in the Sudan, but is of a different nature from that in these cases. It presents as pure right heart failure, usually with a high cardiac output, and is easily recognized. Again, trypanosomiasis occurs in the Sudan, but it has a limited distribution and few of these patients came from infected areas.

Endocardial fibrosis thus appears as a well-defined clinical and pathological condition occurring commonly in Africa in negroes, Arabs, and Europeans alike. It is probably very widespread, and in the past has been labelled chronic ischaemic heart disease. In the Sudan it appears as heart failure for no apparent cause, occurring in adults associated with embolic incidents and usually responding to digitalis and mercurial diuretics. The cases described above have been in middle-aged and elderly patients, but I have seen unexplained cardiac enlargement associated with electrocardiographic abnormalities in younger patients, including children, which may well be due to the same cause.

Addendum.—Since this article was submitted, the paper by Ball *et al.* (1954) on endomyocardial fibrosis has been published. The cases seem to be similar with the exception that those authors found mitral incompetence a common lesion. All cases of mitral incompetence were excluded from the present series, as, in the absence of necropsy, it was impossible to disprove a rheumatic aetiology. On the other hand there were several such cases, and in view of the Makerere findings they may well have been examples of endocardial fibrosis.

Summary

The clinical features of 25 cases of endocardial fibrosis with congestive heart failure occurring in Arabs in the Sudan are described. No clue to the aetiology of the condition was found.

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MAXIMUM URINE CONCENTRATION

BY

B. E. MILES, M.D., M.R.C.P.
Consultant Physician, Hereford

A. PATON, M.B., M.R.C.P.

AND

H. E. de WARDENER, M.D., M.R.C.P.
From St. Thomas's Hospital, London, S.E.1

One of the most easily studied functions of the kidney is its capacity to conserve water under conditions of dehydration. In these circumstances water is reabsorbed from the tubular fluid against an osmotic gradient through the influence of endogenous antidiuretic hormones, and the maximum concentration of the solutes is used as an indication of the kidney's capacity to perform osmotic work. Although osmolarity is the appropriate property which determines the extent to which the solutes can be concentrated, specific gravity is usually measured for clinical convenience. Specific gravity, however, gives only an approximate indication of the osmolarity.

The present paper reports observations on the urines of normal subjects and patients with renal disease, either after 10 to 36 hours' water deprivation or after exogenous "pitressin." The first part of the paper is concerned with the errors which may arise when specific

gravity is measured instead of osmolarity; the remainder deals with some factors concerning the attainment of maximum osmolarity.

Specific gravity was estimated by a standard ward hydrometer, correction being made for a small calibration error and an allowance of ±0.001 being made for each 3° C. variation above or below 15.6° C. at which the hydrometer was calibrated. Detergents were not used for cleansing flasks or urinals. Osmolarity was determined by cryoscopy (depression of freezing-point in degrees centigrade÷1.86=osmols per litre) with a thermometer graduated in 0.01° C; the probable error was less than ±10 milliosmols per litre.

Creatinine output rate was always measured in order to detect errors in urine collection. Creatinine was estimated by Bonsnes and Taussky's (1945) modification of Folin's method.

Urea concentration was determined by the method of Van Slyke and Cullen as quoted by Peters and Van Slyke (1932).

Validity of Specific Gravity as an Indication of Urine Osmolarity

It is generally agreed that the concentration of urine is limited mainly by its osmotic activity or the *number* of particles in solution and that the kidney is indifferent to the *weight* of the solutes. Thus the reabsorption of water by the tubules is opposed to the same extent by a light ion as by a molecule many times heavier. This accounts for the widely appreciated fact that specific gravity (which is a measure of the weight of solutions) is unreliable as an indication of osmolarity when the urine contains substantial quantities of protein or sugar, for these heavy molecules give disproportionately high specific gravity readings. It is not always realized, however, that urines of like osmolarity containing neither of these substances may still show considerable differences in specific gravity.

Fig. 1 plots the osmolarity of more than 200 urines against their specific gravity. It shows that specific gravity is only a rough indication of osmolarity even in normal urines, so that a urine of specific gravity 1017 may be as concentrated, in terms of osmolarity, as a urine of specific gravity 1022, and that the error is greater at higher concentrations. The figure also shows the relatively high specific gravities of urines containing large quantities of sugar or protein, and the relatively low specific gravities of urines with high urea concentrations, collected from subjects after the ingestion of 25 g. of urea.

In addition to this unavoidable error, which is inherent in the use of specific gravity as a measure of osmolarity, there are also avoidable errors due to faulty technique in specific gravity measurement. Calibration errors of 0.002 are common, and urines, when allowed to reach room temperature on a warm day, may give specific gravity readings 0.002 or more lower than would be recorded at the correct temperature. If these errors summate, giving a 0.004 difference from the true figure in a urine which also happens to contain a high urea content (and therefore a low specific gravity in relation to its osmolarity), it will be obvious that the "specific gravity" may give a grossly misleading idea of the urine osmolarity.

Duration of Water Deprivation and the Attainment of Maximum Urine Osmolarity

There seems to be little information on the time taken for the water-deprived subject to achieve maximum concentration of the urine. This will depend, presumably, on many factors, the most important of which are probably the temperature and humidity of the air and the nature and quantity of the food consumed. For a concentration test, different authors recommend periods of dehydration ranging from as little as 12 (Chamberlain, 1951) to as many as 34 hours (Lashmet and Newburgh, 1932) before the onset of the urine collection period.

The following investigation was carried out on 13 convalescent patients under ordinary ward care during the

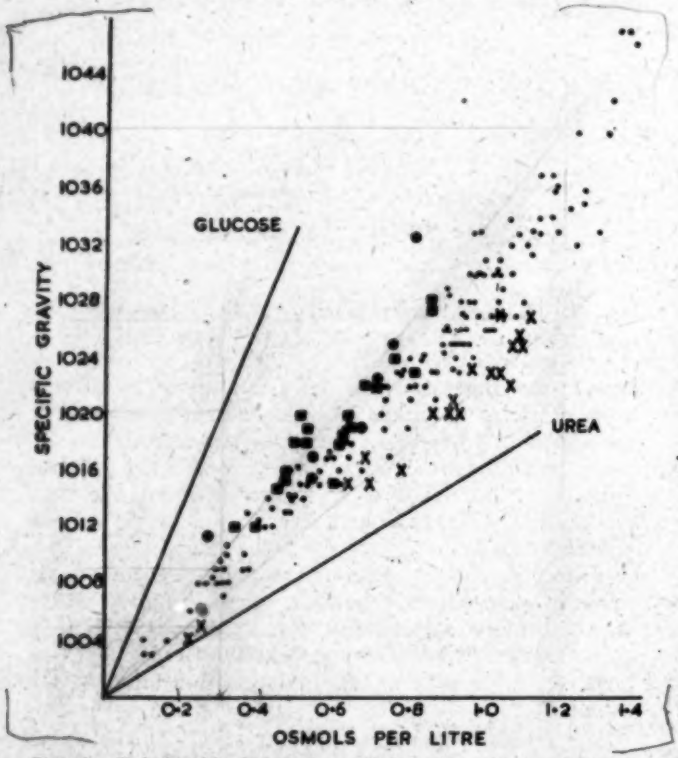

Fig. 1.—Relationship between specific gravity and osmolarity of urine. Different urines are shown as follows: With no sugar or protein (·). With +++ sugar (●). With +++ protein (■). After 25 g. urea by mouth (×). Lines are also given showing the relationship between the specific gravity and osmolarity of glucose and urea solutions.

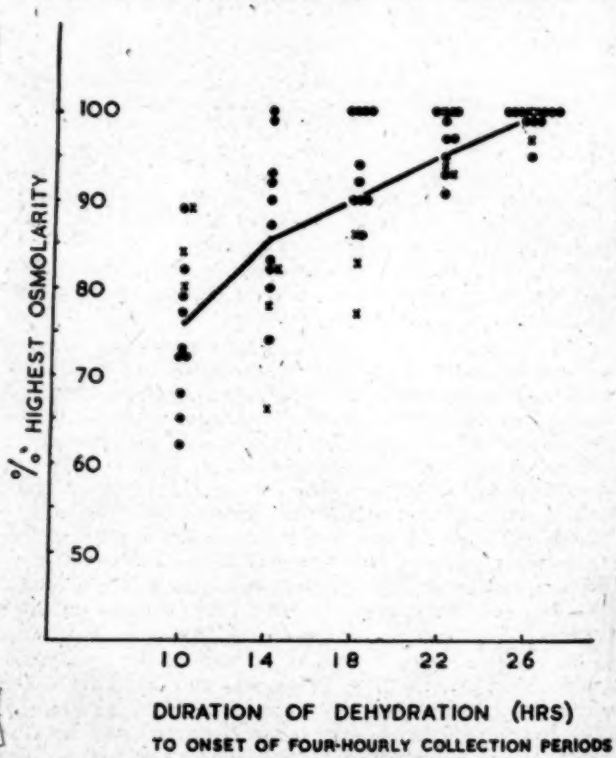

Fig. 2.—Effect of progressive water deprivation on the urine osmolarity in 13 subjects. The osmolarity is expressed as a percentage of the highest osmolarity reached in each subject during 30 hours' dehydration. Urines were collected between 8 a.m. and 4 a.m. in cases marked by a dot, and between 8 p.m. and 4 p.m. in those marked by a cross.

winter; they were considered to have normal kidney function. All were deprived of fluids for 30 hours, but allowed normal food. Four-hourly urine samples were saved during the last 20 hours of this period.

Though it is not claimed that the maximum osmolarity is always reached by 30 hours' dehydration, it is at least clear that it is often not even approached by 14 to 18 hours' (Fig. 2). The results suggest that at least 22 hours' dehydration is desirable to achieve a reasonably accurate idea of maximum osmolarity. The wide scatter of observations after shorter dehydration is equally important; it means that the maximum concentration cannot be predicted from the concentration reached after a short period of dehydration.

Comparison of Urine Osmolarity after 24 to 36 Hours' Dehydration and after Pitressin Tannate

Since a long period of dehydration is necessary to obtain urine of near maximum osmolarity, it would clearly be advantageous if the same effect could be achieved with less hardship to the patient. It was therefore decided to see whether equally good concentration could be obtained by using pitressin. Pitressin tannate in oil was chosen because it acts for many hours and there are no undesirable side-effects. The ampoules were warmed and well shaken before its administration.

Nineteen patients, described in Table I, were studied on two separate occasions. They were either convalescent or in a steady clinical state. Three specimens of urine were collected at four-hourly intervals between 8 a.m. and 8 p.m., on the first occasion after 24 to 36 hours' dehydration and on the second after a subcutaneous injection of 5 units of pitressin tannate in oil at 7 a.m. A moderate amount of fluid was allowed during the second test.

The subjects may be divided arbitrarily into those who after dehydration could concentrate above an approximate level of 850 m.osmols/l. and those who could not. Fig. 3 shows that among the former the effect of pitressin was conspicuously less than the effect of dehydration. In those who could not concentrate so well, however, the effect of pitressin was as good as, or even superior to, the effect of dehydration.

Table I shows a tendency for the osmolarity to increase during the day under both conditions. It is not known whether this was due to increasing dehydration and pitressin absorption respectively, or whether it could be accounted for by a diurnal variation in renal function common to both experiments.

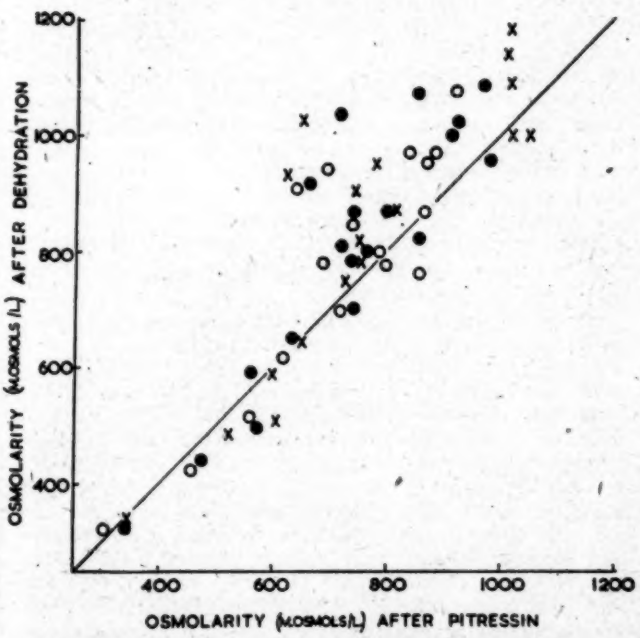

FIG. 3.—Urine osmolarity of morning (O), afternoon (●), and evening (×) specimens after 24 to 36 hours' dehydration and after 5 units of subcutaneous pitressin tannate is compared in 19 subjects (see Table I).

TABLE I.—*Urine Osmolarities of Morning, Afternoon, and Evening Urines in 19 Subjects after 24 to 36 hours' Dehydration and after 5 units of Subcutaneous Pitressin Tannate*

Age	Sex	Diagnosis	Urine Osmolarity (m.osmols/litre)					
			After 24–36 Hours' Dehydration			After 5 Units Pitressin		
			8 a.m. Noon	Noon 4 p.m.	4 p.m. 8 p.m.	8 a.m. Noon	Noon 4 p.m.	4 p.m. 8 p.m.
24	M	Peptic ulcer	958	1,025	1,086	876	923	1,021
62	F	Bronchiectasis	852	855	902	742	745	746
33	M	Eczema	947	1,035	1,024	692	719	651
29	F	Gall-stone	912	915	935	648	663	627
41	M	Peptic ulcer	970	1,000	1,000	885	910	1,020
55	F	Rheumatoid	795	810	950	783	720	780
40	F	Peptic ulcer	970	1,070	1,185	840	855	1,018
28	M	Pneumonia	1,092	1,075	1,130	925	970	1,018
32	M	Peripheral artery disease	870	—	—	803	—	—
43	F	Hepatitis	870	955	1,000	870	980	1,050
61	M	Cirrhosis	755	780	780	678	737	750
48	M	Chronic nephritis	760	818	870	855	852	812
19	F	" "	513	496	510	557	572	662
42	M	Polyarteritis	322	339	328	305	345	340
64	F	Lupus erythematosus	618	645	650	619	640	645
22	M	Chronic nephritis	420	435	480	456	472	528
69	F	Myelomatosis	775	800	820	797	760	760
50	M	Polyarteritis	571	592	588	—	555	599
41	F	Chronic nephritis	702	706	745	715	738	725

Variations in Osmolarity During Progressive Dehydration

The osmolarity of urine during progressive water deprivation does not always steadily increase until a maximum is reached; it may fluctuate considerably (Table II). Further, if the test is repeated under the same conditions of dehydration and times of urine collection considerable differences may occur in the two tests (Table III).

TABLE II.—*Osmolarity and Solute Output Rate of Successive Urines during Progressive Dehydration in Two Subjects*

	Hours of Dehydration					
	10–14	14–18	18–22	22–26	26–30	30–34
1. Osmolarity (m.osmols/l.)	777	1,004	945	936	1,010	1,002
Output (μ.osmols/min.)	576	207	360	243	306	411
2. Osmolarity (m.osmols/l.)	843	935	801	767	890	
Output (μ.osmols/min.)	501	375	492	630	369	

These fluctuations in osmolarity doubtless arise from a variety of causes. They are certainly not always caused by fluctuations in posterior pituitary activity or changes in solute (osmolar) output rate. Hart and Verney (1934) have reported the occurrence of spontaneous diuresis during dehydration which can be abolished by pitressin; several of our examples, however, occurred in dehydrated subjects when under the influence of pitressin tannate. Similarly, though it is well known (McCance, 1945; Rapoport *et al.*, 1949) that a *large* increase in solute output is invariably followed by a reduction in osmolarity in the dehydrated subject, such a fall by no means always followed the

TABLE III.—*Osmolarity and Solute Output Rate of Successive Urines during Progressive Dehydration. The Experiment has been Performed Twice in the Same Subject*

	Hours of Dehydration				
	10–14	14–18	18–22	22–26	26–30
1. Osmolarity (m.osmols/l.)	952	982	1,330	1,175	1,302
Output (μ.osmols/min.)	546	312	324	315	303
2. Osmolarity (m.osmols/l.)	730	973	1,065	1,140	1,180
Output (μ.osmols/min.)	819	267	399	303	390

twofold to threefold increases in solute output which occurred in our cases. Moreover, a fall in osmolarity not infrequently accompanied a *falling* solute output rate (Tables II and III).

Influence of Urea Concentration on the Urine Osmolarity

Preliminary experiments in dehydrated subjects, in whom the osmolar output had been moderately increased by urea or sodium chloride ingestion, gave the impression that a higher osmolarity was maintained after the urea. To test the validity of this observation the following two experiments were carried out on four normal subjects. On both occasions 5 units of pitressin tannate in oil were injected subcutaneously at 11 p.m. and the bladder was emptied an hour later. A further 2.5 units of pitressin tannate were given at 8.45 a.m. and two morning specimens of urine were saved at 9 a.m. and noon. In the first experiment 25 g. of urea in 250 ml. of water and in the second 15–20 g. of salt in 500 ml. of water were taken at 11.30 a.m. In both experiments two or three further specimens were saved during the next four to five hours. Limited quantities of water were permitted to allay thirst. In this way comparable increases in osmolar output were produced by urea and salt, but the urines contained greatly different concentrations of urea.

Of the 36 observations in Fig. 4, 26 urines with higher than average urea content had a higher than average osmolarity, or vice versa, at any given solute output rate. This confirms our previous impression and suggests that maximum

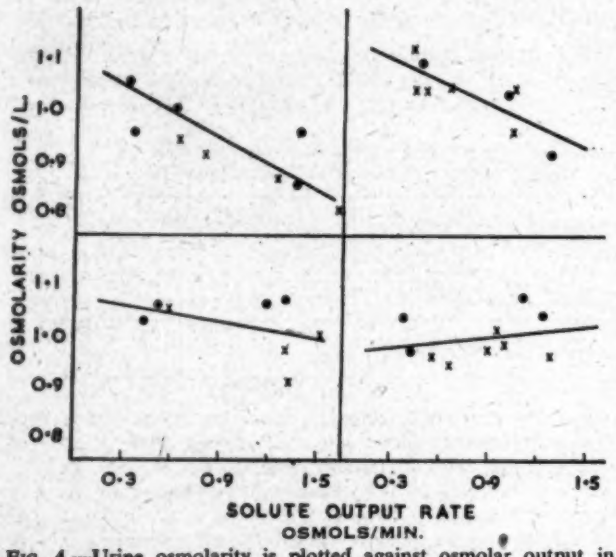

FIG. 4.—Urine osmolarity is plotted against osmolar output in four subjects. Details of the experiments are given in the text. Urines containing a greater than average proportion of urea (urea osmols÷total osmols) are marked by a dot, the remainder by a cross. Calculated regression lines are also shown.

osmolarity may partly depend upon the urea concentration, and that a relatively low urea content may therefore be responsible for some of the unexpected falls in osmolarity which occur during progressive dehydration.

(Statistical analysis of these results must take into account the distance of the points from the regression lines and the extent by which the urea ratios (urea osmols + total osmols/l.) varied from the mean. Calculation shows that the average within-person partial correlation of urea-ratio on osmolarity, with solute output held constant, is 0.48, which differs from zero at a significance level of $P=0.02$.)

Discussion

The measurement of maximum specific gravity as an estimate of renal function is convenient and requires no expensive apparatus. Its value, however, depends on whether specific gravity is a reliable indication of osmolarity, and whether the concentration, after the period of dehydration chosen, is sufficiently near the true maximum.

The first question is the more easily answered. We have shown that even after careful measurement (and errors of 0.004 or more are not uncommon if corrections are not made for calibration and temperature) urines of like osmolarity may vary in specific gravity by as much as 1017–1022, and 1026–1036 (Fig. 1). The greater the concentration of sodium chloride, and particularly of urea, the lower will be the specific gravity at any given osmolarity. This consideration is sufficient indication that more than one specimen should be tested when the specific gravity is borderline.

The second question, concerning the attainment of maximum osmolarity, is more complicated. We have demonstrated that under English winter conditions 14 to 18 hours' dehydration may produce inadequate concentration in a substantial proportion of cases (Fig. 2). This factor alone may mean in practice that a patient who concentrates to only 1016 after 14 to 18 hours may be capable of reaching a specific gravity greater than 1020 after a longer period of dehydration. For this reason we suggest that when precision is required the period of dehydration should exceed 22 hours; Fishberg's (1939) method of carrying out the test seems one of the most suitable and clinically convenient. The patient has no fluids after midday; the bladder is emptied at night and specimens are saved on waking and on two subsequent occasions during the morning. One of these three samples should have a specific gravity of 1022 or more if renal function is normal.

Unfortunately, it does not appear that pitressin can be used routinely in place of dehydration because, in some patients with good renal function the urine concentration after 5 units of pitressin tannate in oil was definitely inferior to the concentration after 24 to 36 hours' dehydration (Fig. 3). This confirms Taylor *et al.* (1945), though in the present experiments twice the amount of pitressin tannate was used, and osmolarity was measured instead of specific gravity. The failure of this theoretically adequate amount to produce maximum concentration is of considerable interest, but we have not enough information to state whether it is due to insufficient pitressin or to differences in hydration. The close correlation of urine concentrations after pitressin and dehydration in subjects with impaired renal function is also similar to the findings of Taylor *et al.* (1945), and suggests that pitressin may be of value in testing the function of patients with known renal disease when dehydration is considered undesirable.

Clinically, of course, it is often not necessary to know the maximum concentration. If after a short period of dehydration or an injection of pitressin the specific gravity reaches 1022 or more, it is clear that renal function is within normal limits. A long period of dehydration is indicated only when such a concentration is not reached by these simpler measures, or when a precise estimate of renal function is required. Further, if in any circumstances a carefully recorded specific gravity of 1018 is obtained, it is unlikely that the patient's symptoms are due to renal failure, though renal disease is not excluded.

The attainment of maximum osmolarity clearly depends on factors other than the length of dehydration, and poor reproducibility of maximum concentration has been commented on by others (Taylor *et al.*, 1945; McCance, 1945). Such factors include differences in solute output rate and posterior pituitary activity, but unexpected falls in osmolarity which may exceed 100 m.osmols/l. (0.003 specific gravity) sometimes occur during progressive dehydration when the solute output rate is *falling* and when pitressin has been administered. We have recorded some evidence that maximum osmolarity depends, among other things, upon the urea concentration. In experiments designed to vary the urea content of the urine we found that the osmolarity tended to be higher at any given solute output rate when the proportion of urea in the urine was above average. The following hypothesis is put forward as an explanation.

If the cells at the most distal site of tubular reabsorption of water were partially permeable to urea, then the "effective" osmolarity of the urea in the urine would be less than that measured by freezing-point depression, the difference varying with the urea concentration. Thus, urines with different urea concentrations might have the same "effective" osmolarity (as regards the tubule cells) but different total osmolarity as measured by freezing-point depression. Selective distal permeability to urea might also permit increased water economy without an increase in osmotic work.

If this hypothesis is correct it may mean that specific gravity is fortuitously a better indication of "effective" osmolarity than we have shown it to be of total osmolarity, for when the urea concentration is high the specific gravity is relatively low.

Summary

The specific gravities of normal urines have been compared with their osmolarities. Considerable variation of specific gravity may occur in urines of like osmolarity.

Dehydration for less than 22 hours gives an unreliable indication of maximum osmolarity.

In some subjects with good renal function 5 units of pitressin tannate in oil produce a urine concentration significantly less than that obtained after dehydration for more than 24 hours. In patients with impaired renal function no difference in concentration is apparent.

Unexplained fluctuations in urine osmolarity occur during progressive dehydration. Possible causes are discussed.

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SOME CURRENT PROBLEMS IN INDUSTRIAL DERMATITIS

BY

F. RAY BETTLEY, M.D., F.R.C.P.

Physician for Diseases of the Skin, the Middlesex Hospital

It seems probable that industrial dermatitis is not decreasing; and the incorporation of industrial insurance in the national insurance scheme has by no means eliminated litigation, although it has altered its mechanism and character. It is often impossible for the physician, whether general practitioner or specialist, to remain entirely aloof from the medico-legal problems which arise. There are three main groups in which the difficulties encountered are mainly or entirely medical.

1. Doubtful Diagnosis

Doubt about the original diagnosis arises principally in distinguishing between eczematous industrial dermatitis and eczematous eruptions of "natural" or "constitutional" origin such as the common nummular or discoid eczema. Many authors—for example, Bettley (1948)—have summarized the salient diagnostic features in these cases, particular attention being given to the site of origin of the eruption and its fluctuation in severity according to changes in or cessation of work. In such a case the family doctor, who has to deal with the case at the outset, is at some disadvantage. He has the advantage, very often, of seeing the onset and studying the earliest appearance of the eruption; but he is usually required to issue a certificate at once and to decide definitely whether the eczema is industrial or not. In some cases it is impossible to do this without a prolonged period of observation, considering the behaviour of the disorder over a period of many weeks or months. To give a firm diagnosis and certificate which has to be altered later gives rise to great dissatisfaction to all parties, not least to the patient, who is likely to feel that his doctor is letting him down. Whenever necessary, therefore, the diagnostic doubt should be very clearly explained to the patient so that he will not feel disgruntled if it is later decided that his disorder is not going to prove a source of income to him. In some such cases, when an early and hasty diagnosis has been amply disproved by subsequent events, the denial of compensation leads to dissatisfaction and a sense of grievance which largely dominates the rest of the patient's life. This unfortunate situation can be avoided by refusal to yield to a demand for exact and firm diagnosis in cases which are still doubtful. In justice to the employer it should be remembered that compensation and damages once paid can seldom be recovered, even though it be proved later that the diagnosis of industrial dermatitis was, from the outset, incorrect.

It is, of course, important to obtain a detailed description of the nature of the patient's work, and of the substances with which he comes into contact; patients are often misinformed about the chemical nature of their contacts, and information should be obtained from the factory manager or chemist if possible. A personal visit to the factory may yield vital information which can be obtained in no other way. No less important is an assessment of possible causes of dermatitis in the patient's home or hobbies. If a housewife develops an eczematous dermatitis it may be, very reasonably, attributed to household detergents; but if, in addition to her own housework, she works as an office cleaner for two hours a day, handling the same detergents, her dermatitis is apt to be labelled industrial, and to be compensated as if her paid employment were the sole cause. The amateur gardener may get dermatitis from handling certain plants; if he is an office worker the correct diagnosis may be reached quickly. But if he is a chemical process worker it is easy to jump to the wrong conclusion and to certify industrial dermatitis; in such a case the diagnosis can often be settled only by a period of observation combined, perhaps, with the results of patch tests.

The prognosis is often of greater concern to the patient than anything else. In general the dermatitis due to a primary irritant clears up in a few weeks, and after some months the skin loses any increased susceptibility to recurrence. Most of these patients can return to their former work provided they take more care than formerly to limit contact with irritants in general, and particularly with the class of irritant which caused their dermatitis.

On the other hand, when there is an allergic hypersensitivity, as can be evidenced by patch tests, the complete avoidance of contact in the future is essential, even if this means permanently abandoning a highly skilled occupation. This type of sensitivity is usually highly specific and relates only to the one substance or perhaps to a group of substances which are closely allied in chemical structure; resistance of the skin to primary irritants in general is not impaired. Unfortunately, many cases, with psychiatric and other factors intervening, do not fall into these clear groups, and in these a period of observation may be required to give the physician a shrewd idea of what the future is likely to hold.

2. The Friction Element

In most cases industrial dermatitis gives rise to comparatively little itching, and visible excoriations are unusual. A certain proportion of patients, however, complain of intolerable itching and even provide a demonstration in the

consulting-room; gross excoriations appear on the skin. As the weeks and months pass the eruption fails to clear up and gradually takes on different characteristics. The skin becomes thickened and lichenified, closely set with excoriated papules of a dusky reddish colour. These extend beyond the parts originally affected and may come to involve large areas on the limbs, face, and less often on the trunk. Those areas originally affected may even recover completely. These patients, more often middle-aged or elderly, are tense, anxious, and dogged by fears that they will never recover. Their claims for compensation usually occupy most of their waking thoughts, and, not above the average in intelligence, they seldom have a clear understanding of the medico-legal issues involved, but pursue their litigation with a strong sense of grievance and with much emotional bias. Temporary improvement in their condition may lead to a return to work, but unless the work is completely to their liking their dermatitis will probably relapse within a short time. Recurrences of their dermatitis are likely to follow any work of a dusty nature; slight exertion is said to bring on excessive sweating and irritation; even the thought of work and the preparation for work is sometimes enough to cause a relapse. Indeed, many of these patients keep reasonably well only while they are away from work and receiving compensation, or if they can find a paid occupation, such as watchman, which involves virtually no work at all.

Although a history of previous emotional maladjustment is not particularly common, these patients are usually unskilled workers who have drifted from one job to another at intervals of a few months or years. It seems probable that they are always people of inadequate personality for whom industrial disease with financial compensation provides a measure of security which, as they approach middle age, is lacking in their lives. Treatment, whether psychiatric or dermatological, is seldom more than palliative and their condition will clear up only if financial compensation is adjusted to their satisfaction. This syndrome may be observed not only in connexion with industrial disease but with other types of compensation—for example, for disease or injuries contracted during military service.

It seems clear that in these cases psychiatric predisposition is the most important causative factor. On the other hand, the law takes the view that the disorder is of industrial origin if the industrial factor formed the essential, final, and immediate cause. In other words, if industrial irritants pulled the trigger it matters little how heavily the gun was loaded. In some of these cases it is evident that the disorder did start as industrial dermatitis; in a great many, perhaps the majority, however, the origins are more difficult to ascertain, particularly if the patient is seen for the first time when the compensation syndrome is well developed. Not only has the objective appearance of the disease then altered, but the patient himself and his attitude to his illness are likely to be very different. After much questioning by doctors and solicitors, combined probably with wishful thinking, the patient himself may evolve an erroneous recollection of the exact way in which his illness began; to this, of course, may be added an additional factor of exaggeration or occasionally deliberate falsification. Thus it is that when objective appearances have become completely altered and the history no longer reliable it may be impossible to say whether or not the disorder was industrial in origin. Almost without exception these patients are given the benefit of the doubt by their doctors and, if the occasion arises, in the law courts. It is concerning these patients particularly that Hewitt (1951) speaks of industrial dermatitis as a psychosomatic disease. At the same time he recognizes that minor trauma may act as a trigger; so also, presumably, may mild chemical damage or a mild attack of true dermatitis.

3. Eczema Sequels

It sometimes happens that an attack of apparently typical eczematous industrial dermatitis is followed, either at once or after a short lapse of time, by the development of eczema elsewhere on the body of a type which would otherwise be considered non-specific or constitutional in origin. An eczematous dermatitis on the hands, for example, may be followed by nummular eczema on the backs of the hands and forearms which is apparently typical both in appearance and in its future behaviour. In such cases a decision must be reached on the relationship between the original dermatitis and the eczema which follows.

In general, it is accepted that nummular eczema is comparatively little affected by contact with irritants, and it is quite unusual for any precipitating cause to be identifiable. When a "dermatitis" case is seen for the first time after the nummular eczema has developed, it is tempting to suppose that the original diagnosis of industrial dermatitis was incorrect, and that the patient has really been suffering from eczema of constitutional origin from the outset. Alternatively, if a period of several months elapses between recovery from the dermatitis and the onset of nummular eczema, most dermatologists would probably prefer to say that there was no connexion between the two disorders. When, however, the eczema follows shortly upon the attack of dermatitis it is difficult to dissociate the two and to say categorically that the eczema would have developed in exactly the same fashion even though the dermatitis had never occurred.

Seborrhoeic dermatitis, appearing for the first time soon after industrial dermatitis, presents a somewhat similar problem. In some cases the latter takes on quite gradually the characteristics of seborrhoeic eczema, and it is impossible to dissociate the two disorders. The seborrhoeic dermatitis then proceeds to run the chronic relapsing course typical of that disorder. The consultant, in these cases, usually has to attempt a retrospective diagnosis and to satisfy himself that the original disease was truly industrial; often he can do no more than guess. It must, of course, be presumed that seborrhoeic dermatitis can be thus provoked only in people who are constitutionally predisposed and that its persistence thereafter is a measure of that predisposition. It seems unsatisfactory that a man should continue to draw compensation for an indefinite period when the "fault" lies so largely with his own constitutional predisposition.

Medical issues of this complexity are seldom debated in the courts. When they are, the diversity of opinion expressed by medical witnesses is often such that a judge has to decide, not by a critical evaluation of the views expounded, but by choosing which witness to believe or by a commonsense estimate of the position. At the least, nobody will venture to assert that the eczema or seborrhoeic dermatitis would certainly have developed when and as it did without the industrial provocation, and this usually puts the decision in the workman's favour. Constitutional predisposition is at best a vague, unassessable, and largely presumptive factor.

Certainly the argument *Post hoc, ergo propter hoc* is likely to arouse so strong a doubt in the legal mind that the patient will receive the benefit of it if he decides to claim that his eczema was the consequence of his dermatitis. It is particularly in this class of case that the most careful attention to details of the history and onset of the disorder may lead to the correct diagnosis.

Medico-legal Considerations

Under the old Workmen's Compensation Act the employee had to prove that he had dermatitis due to the nature of his employment; this done, the employer had to pay compensation in respect of disablement and incapacity to earn wages. Under the National Insurance (Industrial Injuries) Act (1946) the workman has to satisfy the certifying surgeon, and if necessary a medical board, that he has industrial dermatitis; when he has done this, injury benefit is paid at a standard rate from the Industrial Injuries Insurance Fund. On the whole, this latter procedure and the system of appeal works fairly well. There is, as is natural, a tendency for the workman to receive the benefit of the doubt, and it must be very uncommon for a man with dermatitis to be refused compensation. It is, however, by no means so sure that

compensation is as adequate as under the Workmen's Compensation Acts, and that hardship is less common.

Completely separate from this procedure are the regulations made under the Factories Acts (1937 to 1948) and the duty at common law by which the employer has to provide for his employee a reasonably safe system of work and a reasonable degree of protection from industrial skin hazards. Generally speaking, this statutory duty under the Factories Acts is absolute and depends upon the precise terms of the statute or regulations which are framed to provide for individual occupations and industrial risks. The duty at common law was defined by Lord Herschell* in 1891 as follows: "The contract between employer and employed involves on the part of the former the duty of taking reasonable care to provide proper appliances and to maintain them in a proper condition and so to carry on his operations as not to subject those employed by him to unnecessary risk."

The interpretation of this duty admits, evidently, of considerable latitude, and the courts may, and often do, have to decide what are "reasonable" care and "unnecessary" risks.

It is over these matters that a great deal of litigation has taken place in recent years. In these claims the decisions of the certifying surgeon and of the medical and appeal boards are not admissible as evidence, and the workman must bring independent proof that his disorder is indeed industrial dermatitis. After this he seeks to prove that his employer was in some way in breach of his duty and exposed him to undue risk of dermatitis. If he can do this he may be awarded damages of very considerable amount which will take into consideration his degree of suffering and his actual and probable financial loss. The courts often seek medical advice in making this assessment, and doctors should be prepared to help in this respect.

Prevention of Dermatitis

As mentioned above, regulations made under the Factories Acts specify in detail precautions which are to be taken in respect of certain occupations. Apart from this, some general principles are worthy of mention.

In providing a safe system of work an employer must give consideration, firstly, to the nature of the industrial process used and of the substances which are handled; secondly, to the design of plant and apparatus so as to keep workmen as far as possible removed from substances apt to cause dermatitis. In practice, claims are often based on either of these two points. Other matters which the employer may be expected to attend to are:

(1) *Personnel Selection.*—Men who have previously suffered from dermatitis or who are already suffering from a skin disease should not be accepted for employment in an occupation in which dermatitis is at all likely.

(2) Work-places should be properly ventilated, if necessary with special installations to remove dust and fumes.

(3) *Protective Clothing.*—This applies principally to aprons, gloves, and rubber boots. Although, no doubt, these, particularly rubber gloves, will protect the skin from contact with chemicals, they are not always practicable. The wearing of rubber gloves for many hours a day may itself do the skin harm, and some work, such as french polishing, cannot be done when the hands are made clumsy by gloves.

(4) *Barrier Creams.*—The value of barrier creams in certain occupations has been established, but it is easy to overestimate their efficiency. No doubt they limit contact for some time, but their effectiveness may last for only an hour or so, and thus a false sense of security may arise. Apart from this, the use of barrier cream makes the hands easier to cleanse at the end of the shift. This is a very important point, since industrial dermatitis is so often related to over-vigorous attempts at cleaning the hands rather than to the actual substances involved in the work. However, although the medical value of barrier creams is sometimes doubtful, it is difficult to deny that a failure to provide barrier cream implies that an employer has left untaken a simple step to protect his workmen. The cost of barrier cream is likely to amount to less than sixpence a week per workman, and it seems that in most occupations the courts regard an employer as negligent if he does not provide it and take reasonable steps to see that it is used.

(5) Facilities for washing and efficiently cleaning the skin after work must be provided; time must be allowed for this out of the working day; warm water, soap, and towels should be within reasonably convenient access from the workroom. Failure in any of these points is likely to go against an employer even though the connexion between washing facilities and the actual development of dermatitis may not be at all clear from a medical standpoint.

(6) Finally, it is an employer's duty to make sure that his workmen understand the risks of dermatitis in the particular work they are doing; that they understand the precautions that should be taken; and that they know what to do should any sign of skin irritation appear. It has been stated by the Court of Appeal that the employer should ensure through a foreman that employees actually do carry out preventive measures recommended.

Most of these points are dealt with in the Ministry of Labour and National Service Forms 330 and 1863, pamphlets to which the courts rightly attach much importance, though they are in no way obliged to accept them. They give guidance which conflicting medical witnesses rather often, unfortunately, fail to provide.

Under the Workmen's Compensation Acts the employee's compensation was entirely met by the employer, and very substantial lump sums could be obtained from insurance companies in redemption of the employer's liability; common-law actions were therefore seldom necessary before 1948. Since the National Insurance (Industrial Injuries) Act such actions have greatly increased, presumably because compensation under the Industrial Injuries Scheme provides only a comparatively small weekly sum of money, insufficient for the needs of most workmen, and a very small lump sum. It is no doubt right that a man should have means of redress against an employer who carelessly exposes him to risk, and this is not provided under the Industrial Injuries Act. His recourse is to common law.

The hygienic conditions in factories have, of course, been subject to inspection by officers of the Ministry of Labour for many years past, but, although a factory might receive no criticism from an inspector, there were before 1948 many which could be made the subject of complaint if the full scrutiny of the law were brought to bear upon them. The result of the change in the law has no doubt been that employers have in recent years paid greater attention to conditions of work and to the legal as well as the medical value of preventive measures.

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Smith v. Baker & Sons Ltd. Appeal Court.

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Speaking in a debate on cancer research at the Conservative Party Conference last week the Minister of Health, Mr. Iain Macleod, declared, "I give you an absolute undertaking that no new and hopeful line of inquiry will be thwarted through lack of public funds." He was replying to a motion introduced by Mr. J. Warnock, of Hendon South, which stated that the Conference considered that the funds made available by the Government for cancer research were quite inadequate. The motion urged the Government to take more active measures by financial assistance and positive leadership "to inject a real sense of urgency into the search for the cause and cure of this disease." "You cannot buy results," continued Mr. Macleod. "Because you spend twice as much money in this field, it does not mean that you are going to make twice as much progress. I cannot guarantee, nor can anyone else, that however much money you spend you will resolve one of the unsolved problems in the medical field. That is just as true for this terrible scourge of cancer as it is for the common cold—another problem to which we have not yet found the answer."

IDIOPATHIC HYPOCHROMIC ANAEMIA IN MALES

BY

J. W. B. FORSHAW, M.D., M.R.C.P.

Senior Medical Registrar, Whiston Hospital, near Liverpool; lately Medical Registrar, Liverpool Stanley Hospital

Idiopathic hypochromic anaemia is a disease which occurs mainly in females, and its incidence in males appears to be very low. Chlorosis was thought to occur almost entirely in young females, but the following quotations suggest that Shakespeare was aware of the possibility that the disease might appear in males. In *Antony and Cleopatra*, III, ii, 4:

> Caesar is sad; and Lepidus,
> Since Pompey's feast, as Menas says, is troubled
> With the green sickness.

and in *II King Henry IV*, IV, iii, 96, referring to Prince John:

> There's never none of these demure boys come to any proof; for thin drink doth so over-cool their blood, and making many fish-meals, that they fall into a kind of male green-sickness.

From the series of cases which have been reported previously it seems that between 4 and 8% of cases of idiopathic hypochromic anaemia are males. Davies (1931) reported four cases in males out of 55 cases; Britton (1936) reported four cases in males out of 66 cases; and Wintrobe and Beebe (1933) reviewed a total of 498 cases, of which 18 were males. Other published series of cases in males include 26 cases reported by Burger and Witts (1934) and 10 cases by Thomson (1943).

Two recent series of cases have consisted entirely of national service recruits. Shorthouse and King (1951) reported 20 cases among young recruits in the Royal Army Ordnance Corps, and Leonard (1954) detected 47 cases by routine blood examination of 4,221 R.A.F. recruits. The incidence of idiopathic hypochromic anaemia of 1.1% among these R.A.F. recruits suggests that this condition may be more common than has been indicated by the small numbers attending hospital.

The majority of case reports of idiopathic hypochromic anaemia in males have been by British workers. The prevalent opinion of American haematologists, however, is that idiopathic hypochromic anaemia does not occur in males. Heath and Patek (1937) and Wintrobe (1951) believe that hypochromic anaemia in males is almost always due to occult haemorrhage, and Moore (1950) thinks that there is no justification now for the term idiopathic because the cause of the anaemia is always evident. He believes that, while an inadequate diet and poor iron absorption frequently contribute to the pathogenesis of iron deficiency, they do not seem able to precipitate its development unless there is an increased iron loss from the body, and in his experience (1953, personal communication) he has been unable to find a male patient with hypochromic anaemia in whom careful study has revealed no evidence of haemorrhage.

In view of this difference of opinion about the existence of idiopathic hypochromic anaemia in men, 11 further cases are reported, and the aetiology of the condition is discussed.

Review of Cases

The cases were obtained from the records of the David Lewis Northern Hospital, Liverpool, between September, 1948, and September, 1952, and from the records of the Liverpool Stanley Hospital between October, 1949, and January, 1954. All the cases were primarily diagnosed as hypochromic anaemia, microcytic anaemia, or iron-deficiency anaemia, and cases in which the anaemia was obviously secondary to some other disease have not been included. Fourteen cases—six from the David Lewis Northern Hospital and eight from the Liverpool Stanley Hospital—were selected originally, but the follow-up study revealed that in two cases the anaemia was due to carcinoma of the stomach and one case developed haematuria due to benign prostatic hypertrophy, which suggested that the anaemia might have been due to previous persistent microscopic haematuria. Of the remaining 11 patients, one has been followed up for four months, three for between six months and a year, two for between one and two years, two for between two and three years, one for three and a half years, and two for between five and six years. With two exceptions, the patients were all seen personally. Five patients were first seen at the time of their original attendance at hospital and four were first seen at the time of their follow-up attendance.

At the time of their first attendance, nine patients were under the age of 25, and the other two were aged 53 and 61, which is similar to the age distribution in the 26 male patients of Burger and Witts (1934). Lassitude and dyspnoea were the presenting symptoms in eight patients, and of the other three, two boys (Cases 1 and 2) had no definite symptoms of anaemia but were noted to be pale by their parents, and one young man (Case 7) during convalescence from pneumonia was noted to be pale by his doctor.

The tip of the spleen was palpable in four patients, and in one patient (Case 9) there was marked enlargement of both liver and spleen, which led at first to the mistaken diagnosis of Banti's disease. The palpable spleen disappeared in four patients after the anaemia had been corrected, and the other patient, whose spleen is still palpable after correcting the anaemia, has been followed up for only four months. Koilonychia was noted in only one case. There was a loud systolic murmur over the praecordium in three patients, in one of whom (Case 1) it had led to a previous diagnosis of patent interventricular septum. In all of these the murmur disappeared after the anaemia was corrected.

The blood picture showed a severe or moderate degree of hypochromic anaemia in all the patients, and the colour index was always reduced below 0.8 (see Table). The mean

Blood Findings

Case No.	Age	R.B.C. (Millions per c.mm.)	Hb (g.%)	Hb %	Colour Index	W.B.C. (per c.mm.)
1	7	3·8	5·9	41	0·53	10,200
2	14	5·5	8·5	58	0·53	—
3	14	4·5	7·4	50	0·55	8,000
4	14	3·9	8·2	56	0·7	9,400
5	14	4·8	7·0	47	0·48	4,500
6	15	3·8	5·3	37	0·5	11,400
7	19	4·0	6·7	45	0·56	8,000
8	20	3·1	5·8	39	0·62	—
9	24	2·5	4·4	30	0·6	5,700
10	53	3·0	5·6	38	0·63	—
11	61	3·0	7·1	48	0·79	9,600

corpuscular haemoglobin concentration, which was estimated in only three patients, was very much reduced—namely, 19, 19, and 25%. The white-cell count, which was estimated in eight patients, was always within normal limits.

The gastric acidity was estimated in seven patients, of whom six had a histamine-fast achlorhydria and one had hypochlorhydria.

There were no features in the previous history or during the follow-up period to suggest that gastro-intestinal bleeding or steatorrhoea was the cause of the anaemia. In seven patients the faeces were tested for occult blood on several

occasions and the results were all negative. The faecal fat was estimated in two patients and a fat-balance test was carried out on one patient, the results of these investigations being normal. Other possible aetiological factors were teeth extraction, apparently without much haemorrhage, at about the time of the onset of symptoms in one patient, and poor diet in four patients. It is difficult, however, to decide with any certainty whether a diet has an adequate iron content by questioning patients about their menu.

The anaemia was corrected invariably by iron therapy. Nine patients were given oral iron only. One patient (Case 10) was given 1 pint (570 ml.) of blood and intravenous iron initially, followed by oral iron, and one patient was given 2 pints (1,140 ml.) of blood at the onset of treatment, but the subsequent good response to iron therapy showed that the blood transfusion was unnecessary. The reticulocyte response, which was estimated in two patients in whom the anaemia was rapidly corrected by oral iron, was very small —namely, 1% and 1.4%. Sporadic administration of iron before attending hospital was the probable reason for this small reticulocyte response.

The prognosis as regards the anaemia was good and none of the 10 patients who were followed up for longer than six months relapsed. Two of these patients had not taken any medicinal iron during the previous two years, and two had not taken any during the previous year.

Case Reports

The features of the disease are illustrated by the following selection of case reports.

Case 1.—A boy aged 7 was admitted to the Liverpool Stanley Hospital in October, 1953. He was noted to have been pale for several years, and congenital heart disease had been diagnosed previously. He had plenty of energy and there were no symptoms of anaemia. On examination there was pallor of the face and mucous membranes; the tip of the spleen was palpable; there was clinical and radiological evidence of cardiac enlargement; a loud systolic murmur was heard over the praecordium, maximal at the apex; and the nasal septum was deviated, producing nasal obstruction. Laboratory investigations showed: R.B.C., 3,800,000 per c.mm.; Hb, 5.9 g.%; M.C.H.C., 19%; W.B.C., 10,200 per c.mm.; serum calcium, 11.6 mg. per 100 ml.; faecal fat, 7.5%. Occult blood tests on four specimens of faeces were negative. Treatment with "colliron," ½ dr. (1.8 ml.) t.d.s., was started in October, 1953, and produced a reticulocyte response of only 1%. In May, 1954, the mucous membranes were a good colour, the spleen was not palpable, there were no cardiac murmurs, chest *x*-ray examination showed a decrease in heart size to within normal limits, and the Hb had risen to 13 g.%.

Case 3.—A boy aged 14 attended the David Lewis Northern Hospital in November, 1950, complaining of lassitude, dyspnoea, and anorexia for about five weeks. He was taking a poor diet on account of anorexia. The chest *x*-ray examination showed slight cardiac enlargement. A blood count showed: R.B.C., 4,500,000 per c.mm.; Hb, 7.4 g.%; C.I., 0.55; W.B.C., 8,000 per c.mm. He did not take iron therapy as advised, and next attended hospital in September, 1952, when he complained that his symptoms had persisted. On examination the face and mucous membranes were pale, and the tip of the spleen was palpable. A blood count showed: R.B.C., 4,640,000 per c.mm.; Hb, 9.8 g.%; C.I., 0.72. Occult blood tests on two specimens of faeces were negative. There was no excess of faecal fat. A fractional test meal showed histamine-fast achlorhydria. Treatment with 2 tablets of "fersolate" t.d.s. was started in September, 1952, and in November the spleen was not palpable and the blood count was as follows: R.B.C., 4,200,000 per c.mm.; Hb, 12 g.%; C.I., 0.97; W.B.C., 7,200 per c.mm. In April, 1954, he wrote to say that he was feeling well and was in the R.A.F. He had not taken any iron during the last year.

Case 6.—A boy aged 15 was admitted to the Liverpool Stanley Hospital in January, 1954, complaining of lassitude and dyspnoea during the previous two years. His appetite was quite good, but he did not eat meat or fish and only few green vegetables. On examination the face and mucous membranes were pale, the tip of the spleen was palpable, and there was a loud systolic murmur over the praecordium, maximal at the apex. The chest *x*-ray examination was normal. Laboratory investigations: R.B.C., 3,800,000 per c.mm.; Hb, 5.3 g.%; M.C.H.C., 19%; W.B.C., 11,400 per c.mm.; E.S.R., 7-mm. drop per hour; serum calcium, 10.5 mg./100 ml.; fat-balance test normal. Occult blood tests on four specimens of faeces were negative. A fractional test meal showed histamine-fast achlorhydria. Treatment with colliron, 1 dr. (3.5 ml.) t.d.s., was started in February and produced a reticulocyte response of only 1.4%. In May he was feeling very well, and the Hb had risen to 13.3 g.%. The tip of the spleen was still palpable.

Case 9.—A man aged 24 was admitted to the Liverpool Stanley Hospital in August, 1951. He had been discharged from his job because the works medical officer thought he looked very anaemic, but at first he would not admit to having any symptoms. On further questioning, he thought that he had been slightly more breathless on exertion than usual for several months. His teeth had been extracted two months previously, but he did not think that there had been much haemorrhage. On examination there was pallor of the mucous membranes, a systolic murmur was heard at the cardiac apex, and both liver and spleen were much enlarged, so that Banti's disease was diagnosed at first. Laboratory investigations: R.B.C., 2,500,000 per c.mm.; Hb, 4.4 g.%; C.I., 0.6; W.B.C., 5,700 per c.mm. Occult blood tests on faeces were negative. Liver-function tests were normal. Treatment with 2 tablets of fersolate t.d.s. was started in August, 1951, and one month later the haemoglobin had risen to 14.4 g.%. In November, 1952, he was feeling very well, the liver and spleen were not palpable, and the blood count was as follows: R.B.C., 5,500,000 per c.mm.; Hb, 14.8 g.%; W.B.C., 5,800 per c.mm. He had not taken any medicinal iron during the previous year. In April, 1954, he wrote to say that he was feeling well.

Discussion

Idiopathic hypochromic anaemia in males is a rare disease in hospital practice, and only 11 cases were collected from the records of three general medical firms, each containing about 35 beds, over a period of four years. The majority of these patients are below the age of 25, and the diagnosis of idiopathic hypochromic anaemia should not be made in middle-aged and elderly men until they have been followed up for at least a year. The present follow-up study showed that of three middle-aged men who were originally included in the series, two had died from carcinoma of the stomach and one had developed haematuria due to prostatic hypertrophy.

The diagnosis of idiopathic hypochromic anaemia is made in these patients because the aetiological factors are not evident. The cause of the anaemia, however, must be haemorrhage, inadequate iron intake, or poor iron absorption, either together or singly, and these three factors are now considered.

1. *Haemorrhage.*—If haemorrhage produces hypochromic anaemia it is usually chronic and not acute, and so would be expected to continue after the patients attended hospital and to produce a relapse after stopping iron treatment. In none of these patients, however, was there any evidence of haemorrhage during the follow-up period, and the absence of relapse has been a constant feature.

2. *Inadequate Iron Intake.*—The average total daily iron loss in adult men is about 1.2 mg., consisting of 0.4 mg. in the urine (Barer and Fowler, 1937) and 0.8 mg. in the bile (Whitby, 1949). The daily iron requirements for growth are about 0.2 mg. in the 8th year, 0.54 mg. in the 13th year, 0.86 mg. in the 14th year, rising to a maximum of almost 1 mg. in the 16th year, and ceasing completely in the 22nd year (Heath and Patek, 1937). If in normal subjects about 15% of the iron in the intestine is absorbed (Dubach *et al.*,

1948), then adult men require a diet which contains about 8 mg. of iron daily and youths of 16 require a diet containing about 14 mg. of iron daily.

In the National Food Survey for 1950 (Ministry of Food, 1952) it was estimated that the average daily iron intake for adults of both sexes was 13.6 mg., and for a group of adolescents and children it was 13.9 mg. The size of the family, however, influenced the average daily iron intake; it was only 10.9 mg. in families with four or more children. These figures show that even the poorest diet should provide enough iron for adult men and for boys under the age of 14, but that a poor diet may lead to iron deficiency in youths between the ages of 14 and 17, which is the age period when the incidence of the disease is greatest.

3. *Poor Iron Absorption.*—Hawkins *et al.* (1950) found evidence of steatorrhoea in six cases of hypochromic anaemia which were refractory to oral iron therapy, and Badenoch and Callender (1954) have shown that the poor iron utilization in steatorrhoea is due to poor absorption. It should be emphasized, therefore, that intravenous iron preparations should not be given before a trial of oral iron therapy, because the absence of a response to oral iron therapy may be the first evidence which suggests the diagnosis of steatorrhoea. Fat-balance studies were done on only one of the present series of patients, but there was nothing in the histories of the other patients to suggest the diagnosis of steatorrhoea, and they all responded to oral iron therapy.

It has been shown that, except in cases of steatorrhoea, iron absorption is partly controlled by the body's needs for the element and that the average absorption is much higher in patients with hypochromic anaemia than in normal subjects (Brock and Hunter, 1937; Moore *et al.*, 1939; Balfour *et al.*, 1942; Dubach *et al.*, 1948). There is, however, a considerable variation in the amount of iron absorbed by both patients with hypochromic anaemia and by normal subjects (Dubach *et al.*, 1948; Badenoch and Callender, 1954). In these studies, the hypochromic anaemia has usually been due to haemorrhage, which would account for the high average absorption. On the other hand, Balfour *et al.* (1942) found that the amount of radioactive iron which was absorbed by a patient with hypochromic anaemia with no evidence of blood loss was less than the average amount absorbed by patients with anaemia due to haemorrhage, and Badenoch and Callender (1954) found that in a male patient with hypochromic anaemia and no evidence of haemorrhage only 11% of administered radioactive iron was utilized.

In these experiments, which have been discussed, the absorption of iron, which has been given in addition to the normal food, has been studied. However, the work of Moore and Dubach (1951), who measured the iron absorption from foods tagged with radioactive iron, suggests that the absorption of food iron differs from that of medicinal iron salts. They found little difference between the average iron absorption in normal subjects and in patients with untreated hypochromic anaemia, but the variation in the amount of iron absorbed was considerable, ranging between 1.1 and 33.1% (average 6.5%) in 17 normal subjects, and between 1.4 and 17.7% (average 5.8%) in 7 patients with hypochromic anaemia. As they have accepted the amount of iron appearing in the circulating haemoglobin as a measure of the iron absorbed, it is probable that their figures in the cases of hypochromic anaemia are a good indication of absorption, as almost 100% of the absorbed iron is utilized (Dubach *et al.*, 1948). On the other hand, in the normal subjects, in whom less than 50% of absorbed iron is utilized, the iron absorption was probably much more than they calculated in the haemoglobin.

In conclusion, it seems probable that in some patients with hypochromic anaemia the absorption of food iron may be inadequate even when the patient is taking a normal diet, and it is postulated that this is an important aetiological factor in male patients with idiopathic hypochromic anaemia. This view, however, requires confirmation by further studies on iron absorption, using food tagged with radioactive iron. On the other hand, the measurement of the absorption of radioactive iron salts is unlikely to be of value because these patients respond to oral iron therapy.

Summary

Eleven male patients with hypochromic anaemia and with no evidence of haemorrhage or steatorrhoea are described.

All responded to oral iron therapy. None relapsed during the follow-up period, and four of the patients had not taken any iron during the previous year.

The aetiology is discussed, and it is concluded that poor iron absorption and, during adolescence, inadequate iron intake are the aetiological factors.

My thanks are due to the physicians of the David Lewis Northern Hospital and the Liverpool Stanley Hospital for permission to study and follow up their cases. I also wish to thank Sir Lionel Whitby for his permission to publish this paper, part of which was included in a thesis for the Cambridge M.D.

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HAEMOGLOBIN LEVELS OF NORMAL MEN AND WOMEN LIVING IN A TROPICAL CLIMATE

BY

G. R. WADSWORTH, M.D.

(From the Department of Physiology, University of Malaya, Singapore)

There is some doubt about the effects of high environmental temperatures on the haemoglobin level of man. Exposure of a few days to a few weeks are accompanied by a decrease of the haemoglobin concentration (Barcroft *et al.*, 1923; Bazett *et al.*, 1940; Maxfield *et al.*, 1941; Post and Spealman, 1948). The evidence about haemoglobin levels of people who are permanently living in a hot climate is contradictory (MacGregor and Loh, 1941), but it has been shown that such people have normal packed red-cell volumes (Wadsworth, 1952a) and red-cell counts (Wadsworth, 1952b). The present investigation was designed to show if prolonged exposure to high environmental temperature affected haemoglobin levels. The opportunity was also taken to compare haemoglobin levels of different racial groups.

Material

The investigation was made at Singapore, where the environmental temperature varies very little throughout the year and is usually between 23 and 32° C. (73.4 and 89.6° F.), with a humidity of 70 to 90%. There is an absence of

malaria, and the population is in general well nourished. Singapore lies at sea level.

The haemoglobin concentrations of 337 men and 116 women were measured. Their ages ranged from 20 to 40 years, and they had all volunteered to be subjects of the investigation. The group of men consisted of 193 Europeans (57%), 80 Chinese (24%), and 64 other Asians (Indians, Malays, and Eurasians) (19%). The group of women consisted of 72 Europeans (62%), 25 Chinese (22%) and 19 other Asians (16%). It was thought that all were in a good state of health and, where possible, this was checked by a clinical examination. Asian subjects had lived in tropical conditions all their lives, and Europeans for at least six months before the tests.

Methods

Blood was taken from an antecubital vein, using minimal stasis, and was placed in a dry stoppered bottle containing an ammonium-potassium oxalate mixture (Heller and Paul, 1934) to prevent coagulation.

Estimations of the haemoglobin concentration were made within a few hours of collecting the blood, except in a few instances when there was a delay of 24 hours. In the latter circumstance specimens were stored at 4° C. until required, but it has been shown that this did not materially affect the accuracy of the estimations (Wadsworth and Lee, 1954).

Haemoglobin concentrations were estimated from the light transmission of oxyhaemoglobin solutions by means of a Spekker absorptiometer (Hilger, 1946) using OGRI filters. The instrument was calibrated against the total iron content of blood by the method of Wong (1928), and this was checked against estimations of the oxygen-combining capacity by the method of Van Slyke and Neill (1924). It was observed that the same relations of haemoglobin to iron and haemoglobin to oxygen capacity as were found by King and Gilchrist (1947) held for blood from Europeans and Asians in a tropical climate; and that the oxygen/iron ratio was the same as that found by Gibson and Harrison (1946) in England. Oxyhaemoglobin solutions were made by dissolving 0.1 ml. of blood in 20 ml. of 0.1% anhydrous sodium carbonate. The calibration of the pipettes was checked and found accurate. Before dilution the blood was thoroughly mixed by rotating the bottle between the palms of the hands for three minutes. In a separate investigation this treatment was found to produce adequate mixing. Further details of the method of estimating haemoglobin are reported elsewhere (Wadsworth and Lee, 1954).

A permanent cyanhaematin solution was prepared by dissolving an appropriate amount of blood in a cyanide solution recommended for use in the Tropics (Cheek, 1950). The cyanhaematin was placed in a glass cell, which was then sealed. The reading given to this preparation when placed in the absorptiometer was checked before each series of haemoglobin estimations and was found to be constant. Calibration curves were made on different occasions, and these provided further evidence that the absorptiometer gave constant readings throughout the investigation.

Details of the results are given in the Table. The differences between group means for both males and females were not statistically significant.

Haemoglobin Levels of Normal People Living in Singapore

Racial Group	No.	Mean Hb g./100 ml.	S.D. g./100 ml.	S.E. of Mean	"t" (Compared with Hb of Europeans)	P
Males:						
Europeans ..	193	16·03	1·58	0·1136		
Chinese ..	80	16·23	2·14	0·2392	0·8	<0·3
Indians ..	33	16·60	3·17	0·5519	1·6	<0·1
Other Asians	31	15·87	3·07	0·5524	0·5	<0·6
Total ..	337	16·12	1·11	0·0604		
Females:						
Europeans ..	72	13·80	1·84	0·2170		
Chinese ..	25	13·95	3·12	0·6240	0·3	<0·7
Other Asians	19	14·07	3·47	0·7950	1·1	<0·2
Total ..	116	13·88	1·62	0·1505		

Discussion

The mean haemoglobin concentrations found in the present investigation agree closely with those generally accepted as normal for people living in temperate climates (Whitby and Britton, 1950; Wintrobe, 1951). Statistical comparison of the present figures for Europeans with those of a recent investigation on comparable subjects living in England (Berry *et al.*, 1952) showed that the difference was not statistically significant for men ("t"=0.7, P<0.4) or for women ("t" =1.3 P<0.1). It was concluded that the present investigation provided no evidence of a climatic effect on haemoglobin levels.

It was found by previous investigators that when men stayed for two to three days in a hot room there was a fall in the packed red cell volume or haemoglobin concentration (Bazett *et al.*, 1940; Spealman *et al.*, 1947; Glaser, 1949; Stein *et al.*, 1949). This fall may have been due to an increase in total plasma volume which was found to take place in conditions of environmental warmth (Barcroft *et al.*, 1923; Forbes *et al.*, 1940), although the evidence for this is not conclusive (Stein *et al.*, 1949). The findings of the present investigation suggest that when people stay for months or years in a warm climate haemoglobin concentrations are adjusted so that they become the same as those of people living in a cool climate.

In the present inquiry there was no racial difference in haemoglobin levels, although MacGregor and Loh (1941) found in Singapore that Asians had lower haemoglobin concentrations than Europeans. This discrepancy may be explained by the fact that these investigators were examining subjects of a different social grade than those of the present investigation, or that the nutrition of Asians in Singapore has improved since their investigation.

Summary

The haemoglobin levels of 337 men and 116 women of different races living in Singapore were measured.

The mean haemoglobin concentration of men was 16.12 g. per 100 ml. and that of women was 13.88 g. per 100 ml.

There was no evidence of a racial difference in haemoglobin levels.

The present findings suggest that the fall in haemoglobin levels observed by other investigators in men who stayed in hot rooms for several days was a temporary effect, and that normal people who stayed for months or years in a hot climate had normal haemoglobin levels.

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NASAL CARRIAGE IN STAPHYLOCOCCAL SKIN INFECTIONS

BY

L. G. TULLOCH, M.D.

Senior Registrar (Dermatology) Bristol Royal Hospital

The treatment of chronic staphylococcal infections of the skin is seldom rewarded by the satisfaction of a really permanent cure, even after the delivery of mighty broadsides from our armamentarium of modern antibiotics. The main reasons for this, I would suggest, are threefold:

(*a*) *Constitutional.*—In some individuals favourable conditions are provided for the growth of staphylococci by virtue, for example, of a hormonal imbalance (especially androgen excess) or a metabolic imbalance (with particular reference to the sugar and water content of the skin). One cannot hope to alter these factors permanently.

(*b*) *Immunity.*—Active immunization against *Staphylococcus pyogenes* is, on the whole, disappointing. Favourable results have, however, been reported with vaccines and with toxoid, especially with the latter (Barber and Forman, 1933; Dolman, 1935; Whitby, 1936; Bocage, Mercier and Pillet, 1947; and others). There is much need for research in this field, and there are reasons for hoping for improvements in the immunological attack, but detailed discussion of this is beyond the scope of this article.

(*c*) *Nasal Carriage.*—There is abundant evidence to suggest that staphylococci flourishing in the anterior nares provide the source of infection, and of reinfection after local treatment, in most staphylococcal skin diseases. The anterior nares have been demonstrated to harbour staphylococci in greater profusion than any other part of the body and in a very high percentage of the population. Nasal carriage of staphylococci was first demonstrated by Danbolt (1931), and since then many others have carried out investigations to determine the incidence in the general population. Miles, Williams, and Clayton-Cooper (1944), in a sample of a working-class population, obtained a mean carrier rate of 47.4%; and Williams (1946), taking a series of eight weekly swabs from each of a number of individuals, obtained an average carrier rate of 63% for any one week, and a total carrier rate over the eight weeks as high as 89%.

It will be obvious, therefore, that sterilization of the anterior nares must be a corollary to other methods of treatment if indeed the bacteria responsible do originate from the nasal flora. McFarlan (1938), however, has drawn attention to the fact that the frequency of the presence of staphylococci in the noses of healthy individuals makes it possible that their presence in the noses of patients with staphylococcal infections might merely be a reflection of the carrier rate in the community, and that, before attaching any significance to such findings, the identity of the types would have to be proved. Professor Robert Cruickshank (1953), in his Malcolm Morris Memorial Lecture (December, 1951), voiced his suspicion of the nose as the source of infection in staphylococcal impetigo and stressed the need for the determination by phage-typing of the source of the infecting organism.

Miles *et al.* (1944) took the first step in this direction by phage-typing the nasal and skin strains from 16 persons; in 15 of these the strains proved to be identical. Williams (1946) produced similar results: 31 out of the 36 double (nasal and skin) carriers had identical strains present in the nose and on the skin. This double carriage of identical organisms offers strong presumptive evidence that the nose is the source of staphylococcal skin infections. All that remains to be done is to prove the identity of strains obtained from the nose and from actual skin infections in the same individual. Hobbs, Carruthers, and Gough (1947) provide further evidence by the serological typing of strains from the nose and from facial lesions in 19 patients, 17 of whom had staphylococci in the nose, in each case of the same serological type as in the lesion. The numbers involved in this investigation are small, but the results are striking enough to be worthy of note.

A search of the literature revealed no report of any investigations in which strains from the skin lesions and from the nose were compared by phage-typing. I therefore collected a total of 73 pairs of cultures from the noses and lesions of patients suffering from sycosis barbae, furunculosis, folliculitis, and infective eczematoid dermatitis; these were typed and the results obtained are tabulated below. Since completing this work an account has been published by Valentine and Hall-Smith (1952) of a similar series, totalling 25 cases, which closely approximates to the results obtained by myself. In 19 cases the strains were identical, and in five probably identical. Unfortunately, details of the phage types are not given.

Phage-Typing

The cultures used in this investigation were obtained from a consecutive series of patients seen by me at the Manchester and Salford Hospital for Diseases of the Skin. No system of selection or rejection was employed.

Two swabs were taken from each patient—one from the anterior nares, and one from the boil, pustule, bulla, or under the crust in the eczematoid lesions. Cultures were made from these on blood-agar plates and incubated overnight at 37° C. In most cases well-pigmented aureus colonies of *Staph. pyogenes* were grown, although in a few cases coagulase-negative strains were found. Almost invariably the strains isolated from the nose and from the lesion in the same patient presented an identical appearance in colony, size, colour, and the amount of haemolysis produced. Subcultures were made in nutrient agar, and these were kept for typing.

In the earlier stages of this investigation I grew the phages from filtrates and propagating strains kindly supplied by the Public Health Laboratory Service. Later, when facilities were not available for propagation, the Central Public Health Laboratory was good enough to undertake the typing of the remaining strains to complete my series. The typing was carried out with the method described by Wilson and Atkinson (1945). The results are tabulated below. All the strains listed were coagulase-positive.

Results

The key to the symbols used is as follows: The phage numbers represent phages producing confluent lysis. + represents additional minor reactions. NT indicates that the strain is not typable. W indicates weak reaction.

Sycosis Barbae.—Thirty cases were investigated. In seven of these neither strain was typable. In the remaining 23 the results were as shown in Table I.

Furunculosis and Folliculitis.—Thirty-three cases were investigated. In nine of these neither strain was typable. In the remaining 24 the results were as shown in Table II.

Infective Eczematoid Dermatitis.—Ten cases were investigated. In two of these neither strain was typable. In the remaining eight the results were as shown in Table III.

Of the 73 pairs of strains examined, 18 pairs were not typable, in 4 only one strain was typable, and in 51 both strains were typable. In 45 (88.2%) of these 51 pairs both strains were identical. In the various types of infection the

TABLE I

Case No.	Staphylococcal Phage Types: Nose	Skin Lesions
1	6, 47, 54	6, 47, 54
2	7+	7+
3	54+	54+
4	6, 47, 54+	6, 47, 54+
5	54	54
6	7, 47c, 54+	7, 47c, 54+
7	7, 54+	7, 54+
8	47+	47+
9	7, 47, 54+	7, 47, 54+
10	7, 42b, 42e, 54+	7, 42b, 42e, 54+
11	7+	3b, 3c+
12	52a+	52a+
13	52a+	52a+
14	52a	52a
15	52a	52a
16	3b, 3c	3b, 3c
17	42e	42e
18	42e	42e
19	53, 31	53, 31
20	31+	31+
21	51+	51+
22	6, 47, 54+	NT
23	47, 54	NT

TABLE II

Case No.	Staphylococcal Phage Types: Nose	Skin Lesions
1	7, 47, 54+	7, 47, 54+
2	47, 54+	47, 54+
3	6, 47+	6, 47+
4	7, 47, 54	52a
5	47, 54+	47, 54+
6	7+	7+
7	47, 53, 54+	47, 53, 54+
8	31, 54	31, 54
9	52a	52a
10	3b, 51+	3b, 51+
11	3b, 3c, 31+	3b, 3c, 31+
12	3c+	3c+
13	3b, 3c+	3b, 3c+
14	3b, 3c, 31, 52a	3b, 3c, 31, 52a
15	3c+	3c+
16	51	51
17	51+	51+
18	42e	42e
19	42e	42e
20	31, 44	47+
21	31, 53+	44+
22	53+	52, 53W, 55a
23	3b+	NT
24	6, 47, 54	NT

TABLE III

Case No.	Staphylococcal Phage Types: Nose	Skin Lesions
1	7+	7+
2	54	54
3	54	54
4	31, 47	31, 47
5	31+	31+
6	3c+	3c+
7	3c	6, 47+
8	3b, 3c+	3b, 3c+

results were: (*a*) sycosis barbae, 20 (95.2%) out of the 21 typable pairs were identical; (*b*) furunculosis and folliculitis, 18 (81.8%) out of the 22 typable pairs were identical; (*c*) infective eczematoid dermatitis, 7 (87.5%) out of the 8 typable pairs were identical.

The two commonest groups of phage types encountered in the series were the 6/7/47/54 group and the 3b/3c group, which between them account for two-thirds of the total where typing was possible (46% and 20% respectively). Noteworthy also is the relatively small number of 3b/3c group in the sycosis series, and the absence of the 52a group in the infective eczematoid dermatitis series. Comparison with phage types found in other areas, such as those reported from St. Thomas's Hospital by Elwood (1951), suggests that there may be a geographical variation in the incidence of different phage types.

Discussion

These figures provide the final link in the chain of evidence proving the identity of the strains of staphylococci isolated from a skin infection and from the anterior nares of the same patient. It would therefore seem that the nose is the primary source of infecting organisms in most cases of chronic staphylococcal dermatoses. Moreover, these findings would suggest that local treatment alone, although temporarily successful, unless accompanied by an attack on the nasal flora, is likely to be followed by a relapse of the infection. There are various methods by which sterilization of the anterior nares may be attempted. One which I have found useful for this purpose is the tyrothricin solution described by MacKee *et al.* (1946). Their formula is:

Sodium mixed alkyl sulphonate	1.0%
Tyrothricin	0.1%
Propylene glycol	10.0%
Distilled water	88.9%

This vehicle was found to increase the penetration of the tyrothricin. Alternatively, an aqueous solution of penicillin (1,000 units per ml.) is very effective, and, in spite of the risk of sensitization usually attached to the topical use of penicillin, I have yet to see it occur following the use in this way of an aqueous solution. These solutions are best administered with an atomizer, but, as this may not always be convenient, a suitable cream containing 0.1% tyrothricin or 1% aureomycin may be used. Tyrothricin is especially suitable for this purpose, as it is never administered parenterally; the risk of producing resistant strains may therefore be ignored.

Summary

A brief account is given of the relevant studies in staphylococcal carriage.

A report is made of an investigation establishing, by phage-typing, the identity of strains of staphylococci carried in the anterior nares and those isolated from infections of the skin.

The importance of adequate sterilization of the anterior nares in the treatment of staphylococcal skin infections is stressed, and methods of doing this are suggested.

I am indebted to the consultants of the Manchester and Salford Hospital for Diseases of the Skin for permission to investigate these cases; also to Professor H. B. Maitland, of the department of bacteriology, Manchester University, for the provision of laboratory facilities and for his encouragement and help. I wish to thank Dr. R. E. O. Williams, of the Central Public Health Laboratory, for undertaking the typing of the latter part of my series of staphylococcal strains. Part of the material in this article was incorporated in a thesis for the degree of M.D. (Aberdeen).

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The Ceylon Ministry of Health has asked the World Health Organization for the services of five international experts to establish in Colombo a third nurses' training school. The nursing team asked for consists of a principal for the school, a nursing arts instructor, a public health educator, a paediatrician, and a nurse. The Ministry has suggested that the contract of the W.H.O.'s staff working now in the nurses' training school in Kandy should be extended when it expires next year and that they should be transferred to Colombo. Other requests made to W.H.O. for new projects in 1956 include a consultant in preventive mental health for the mental health services and an epidemiologist for the Angoda fever hospital. These requests, which were put before the recent meeting of the Regional Committee for South-east Asia, were presented by Dr. D. L. J. KAHAWITA, director of Ceylon's health services.

AUREOMYCIN AND ERYTHROMYCIN THERAPY FOR STR. PYOGENES IN BURNS

BY

E. J. L. LOWBURY, B.M.

AND

J. S. CASON, F.R.C.S.Ed.

Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital

In an earlier report (Jackson, Lowbury, and Topley, 1951), aureomycin and oxytetracycline ("terramycin"), given by mouth, were shown to be effective in eliminating *Streptococcus pyogenes* from burns. Oral aureomycin has since then been our routine treatment for such infection; the organisms have nearly always been absent from swabs taken five or seven days after treatment was started, and usually have not reappeared later.

Occasionally burns were not cleared of *Str. pyogenes* by such treatment, and the streptococci isolated have been found moderately resistant to aureomycin and oxytetracycline; all of them, however, were sensitive to penicillin and also to erythromycin. Penicillin applied locally is valuable as a prophylactic agent, and for this reason has been adopted as a routine application for burns (Jackson *et al.*, 1951). In established streptococcal infection of burns, however, its value as a therapeutic agent is limited, probably because of penicillinase-producing organisms in the same burn (Cruickshank, Squire, and Topley, 1948; Jackson *et al.*, 1951). Erythromycin seemed to us the most suitable alternative for the treatment of infections with streptococci resistant to aureomycin and oxytetracycline. Previous work (Heilman *et al.*, 1952; Haight and Finland, 1952) has shown the value of erythromycin against *Str. pyogenes* both *in vitro* and in throat infections.

We have therefore made a trial, in which oral aureomycin and erythromycin were compared in the treatment of burns infected with *Str. pyogenes* sensitive to both antibiotics. We also describe in this paper the clinical value of chemotherapy for *Str. pyogenes* as shown by the effect of aureomycin treatment on the result of grafting operations.

Comparison of Aureomycin and Erythromycin

Conduct of Trial.—During a period of eight months oral aureomycin or erythromycin was given for six days to patients over 1 year of age on the appearance of streptococci of Lancefield's group A (*Str. pyogenes*) on any burn. Cases were admitted alternately to the erythromycin and the aureomycin treatment groups. Separate lists were kept for patients treated by the exposed and by the covered methods. A few patients with aureomycin-resistant streptococci on their burns were treated with erythromycin but not included in the controlled trial.

Dosage.—For patients over 6 years of age the dosage was 600 mg. of erythromycin or 1 g. of aureomycin daily; those under 6 years of age were given 400 mg. of erythromycin or 500 mg. of aureomycin daily, usually as a suspension. A few patients were given a slightly lower daily dosage of erythromycin (400 mg. for adults and 300 mg. for children). Erythromycin was given as "ilotycin" tablets and paediatric preparation, and occasionally as "erythrocin" tablets. In a few cases the course of treatment was prolonged beyond the sixth day for clinical reasons. In some of the cases treated with aureomycin the course was curtailed to four days on account of vomiting and diarrhoea.

Bacteriology.—Swabs taken from burns at all dressings and operations, and daily from those treated by the exposed method, were examined by the methods previously described (Jackson *et al.*, 1951). Haemolytic colonies were subcultured and grouped by Lancefield's method. A proportion of the group A streptococci were typed at the Oxford Public Health Laboratory. All strains of *Str. pyogenes* were tested for sensitivity to erythromycin, aureomycin, oxytetracycline, and penicillin by a tube diffusion test (Hurst, 1954), and a proportion were also tested by a tube dilution test. The sensitivity to these agents of *Staphylococcus aureus* from all burns in the ward was also tested, so that the emergence and spread of resistant variants could be detected.

Results of Trial.—Table I shows that all the burns in the trial were free from *Str. pyogenes* after three or more days' treatment with erythromycin or aureomycin. A slightly larger proportion of burns in the erythromycin than in the aureomycin series did not show *Str. pyogenes* during the first three days of treatment. Reappearance of streptococci on burns from which the organisms had been cleared was infrequent (3 out of 24 in the erythromycin, 5 out of 24 in the aureomycin series). All of seven burns (on five patients) from which aureomycin-resistant streptococci had been isolated were free from streptococci after a course of treatment with erythromycin. Two of these patients had had previous treatment with aureomycin, at the end of which streptococci were still found in the burns. The value of erythromycin is inferred from the results of this trial by the fact that it was as effective as aureomycin, which had been found effective in a previous trial (Jackson *et al.*, 1951). We used a dosage of erythromycin smaller than that commonly recommended—for example, Haight and Finland (1952). No toxic effects were noted in the patients receiving erythromycin.

TABLE I.—*Comparison of Erythromycin and Aureomycin Therapy for Burns Colonized with Str. pyogenes*

	Burns of Patients Treated with			
	Erythromycin		Aureomycin	
	Streptococci Present	Streptococci Absent	Streptococci Present	Streptococci Absent
At end of course, or after 3 days' treatment ..	0	24 (100%)	0	24 (100%)
During first 3 days of course ..	4	13 (76%)	6	7 (54%)

Note.—In each series there were 24 burns in 21 patients.

Sensitivity of Str. pyogenes to the Antibiotics

With the exception of the seven aureomycin-resistant strains mentioned above, all the streptococci isolated from patients in the trial were sensitive to aureomycin and oxytetracycline (minimal inhibitory concentration 0.4–0.8 μg. per ml.), and to erythromycin (minimal inhibitory concentration 0.5 μg. per ml.).

Streptococci resistant both to aureomycin and to oxytetracycline have been isolated from burns in this unit on three occasions during the past year. On the first and third occasions they appeared in the burns of one patient only and did not spread to others in the same ward. In each case the patient was being treated with aureomycin for an infection with aureomycin-sensitive streptococci, but the organisms were found to persist after treatment and to have become resistant to aureomycin and to oxytetracycline. The strains of *Str. pyogenes* isolated from these two cases were of types 3 and 9 respectively, and it was found that in each case the serological type was the same in the sensitive strain isolated before aureomycin therapy and in the resistant strain isolated after. It seemed most likely, therefore that in these cases resistant variants had emerged on burns during

the course of aureomycin therapy. On the second occasion when aureomycin-resistant streptococci appeared, they were of type 9 and spread from a patient treated with aureomycin to four other patients in the same ward who were not receiving the antibiotic.

No aureomycin- and oxytetracycline-resistant streptococci were found in the nose or throat of any patient or member of the staff on any of these occasions. All strains of *Staph. aureus* isolated during the trial were sensitive to erythromycin. Since then erythromycin-resistant staphylococci have appeared on the burns of several patients, most of whom were at the time having a course of erythromycin therapy. Further details about these organisms will be reported elsewhere.

The minimal inhibitory concentration of oxytetracycline and of aureomycin towards the resistant streptococci was 12.5 μg. per ml. On subculture of the tubes showing inhibition to large volumes of broth, growth of a sensitive strain was obtained from aureomycin concentrations up to 25 μg. per ml. and from oxytetracycline concentrations up to 400 μg. per ml.; resistant streptococci were obtained from aureomycin concentrations up to 50 μg. per ml. and from oxytetracycline concentrations up to 200 μg. per ml. By these tests sensitive and resistant streptococci appeared to have the same low sensitivity to the bactericidal action of aureomycin and oxytetracycline.

Attempts to induce resistance to oxytetracycline by subculture through increasing concentrations of the antibiotic were unsuccessful with 10 streptococci, including a sensitive type 9 organism isolated from a burn on which resistant streptococci appeared later.

Clinical Value of Therapy for Str. pyogenes in Burns

The importance of *Str. pyogenes* as a pathogen in burns is widely recognized, and an association between its incidence and the failure of skin grafts, delayed healing, and other adverse effects has been noted (Bodenham, 1943; Clarkson and Lawrie, 1946; Jackson *et al.*, 1951). The association of adverse results with a higher incidence of a particular organism is, however, inadequate evidence of its pathogenicity.

The pathogenic action of *Str. pyogenes* on burns, suggested by the results of a prophylactic trial of penicillin (Jackson *et al.*, 1951), receives further support from the grafting results in a series of burns cleared of *Str. pyogenes* by aureomycin, and a collateral series in which aureomycin was not given or was started less than three days before the grafting operation. The patients in this comparison (not a controlled trial) were comparable in respect of age, sex, and area of burn. Table II shows that in 11 out of 44 (25%) burns of patients treated with aureomycin skin-grafting operations failed (< 80% "take"), compared with 16 out of 18 (89%) failures in burns of patients to whom no aureomycin was given before the operation ($\chi^2 = 18.8$; $P < 0.001$). A high proportion of failures (7/9, or 78%) was found also in burns colonized by *Str. pyogenes* when treatment with aureomycin was started less than three days before the operation. It seems most likely that these results are related to the presence or absence of *Str. pyogenes* at the time of operation.

TABLE II.—*Aureomycin Therapy for Burns with Str. pyogenes and Results of Subsequent Skin-grafting*

Treatment	Results of Skin-grafting				*Str. pyogenes* in Burn 1–7 Days after Operation		
	80% or More "Take" (Success)	Less than 80% "Take" (Failure)	Total	% Failures	Present	Total	% Present
Aureomycin started 3 days or more before operation	33	11	44	25	4	40	10
(*a*) Course stopped before operation	12	5	17	29	3	15	20
(*b*) Course continued after operation	21	6	27	22	1	25	4
Aureomycin started less than 3 days before operation	2	7	9	78	4	9	44
No aureomycin given before operation	2	16	18	89	11	18	61

Interference by *Str. pyogenes* with skin-grafting and healing of deep burns makes it important to eliminate this organism by chemotherapy when it breaks through the prophylactic barrier of penicillin. For this purpose oral aureomycin and erythromycin are both very effective, the latter having been effective also on three occasions when aureomycin-resistant streptococci emerged during treatment with aureomycin.

It is desirable that erythromycin should not be used when other antibiotics are equally effective, in order to prevent (or at least delay) the emergence of erythromycin-resistant staphylococci. We would advocate the use of erythromycin for the treatment of streptococcal infection of burns in severely ill patients whose recovery might be jeopardized by the toxic side-effects commonly found during aureomycin therapy; but in such patients frequent examination of the burns and nares for staphylococci resistant to erythromycin is advisable.

Summary

A comparison of oral erythromycin and oral aureomycin therapy for elimination of *Str. pyogenes* from burns has shown that the former antibiotic is as effective as the latter.

Streptococci resistant to aureomycin and oxytetracycline occasionally emerged during treatment with aureomycin, but retained their sensitivity to erythromycin and penicillin and were eliminated from burns during a course of treatment with erythromycin.

The clinical value of chemotherapy for *Str. pyogenes* is demonstrated in the case of aureomycin by improved results of skin-grafting operations, provided therapy begins at least three days before the operation.

We wish to thank the Medical Research Council Antibiotics Clinical Trials Committee and Messrs. Eli Lilly for supplies of erythromycin; the Oxford Public Health Laboratory for typing a number of streptococci; Mr. L. Hurst for assistance and information; and members of the nursing staff at the Birmingham Accident Hospital for their co-operation.

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Co-operation between parents and the local health authority is a vital factor in helping mentally deficient children who live at home, said Miss PATRICIA HORNSBY-SMITH, M.P., Parliamentary Secretary to the Ministry of Health, in opening a new occupation centre at Mansfield on October 6. Family life was as valuable to the mentally handicapped as it was to others, she continued, and the public was alive to the need for a good all-round domiciliary service. At the beginning of this year there were 244 occupation and training centres for mental defectives, compared with 180 in 1939 and only 100 in 1948. The number receiving training at the centres was well over 9,000, and some 1,600 were receiving training in their own homes. The provision of facilities was a major problem for local authorities, especially in rural areas. Miss Hornsby-Smith paid tribute to the excellent work being done by the National Association of Parents of Backward Children.

Medical Memoranda

Two Cases of Injury to the Femoral Artery

The following two cases are thought to be worthy of record on account of the rarity of injury to the femoral artery.

Case 1

A butcher aged 35 was disarticulating a joint when the knife he was using—a short one with a sharp point—slipped and he sustained a punctured wound in the right groin. Haemorrhage was profuse. The accident happened at about 8 a.m., and he was admitted to the hospital at 8.10 a.m. On arrival he was pulseless and still bleeding from the wound, which was just below Poupart's ligament. There was swelling of the groin as a result of a large haematoma. Steps were taken to control the bleeding by pressure. He was given an immediate intravenous transfusion of dextran—4 pints (2.3 litres) rapidly in one hour. His condition improved, and he was transferred to a surgical ward at 10 a.m.

Operation (12.30 p.m.).—By this time, four and a half hours after the injury, 5 pints (2.8 litres) of dextran had been given intravenously. Blood transfusion was started. Care was taken not to remove any dressings until the patient was anaesthetized and on the operation table, and preparations had been made to deal with the condition found. On removing the dressings there was a gush of blood. The bleeding was controlled by digital pressure and the field of operation was prepared. The common femoral, the superficial femoral, and the profunda arteries were then exposed by an incision below the site of digital pressure, and the common femoral artery was controlled by means of a clamp. A perforated wound of that artery was demonstrated at the junction of the middle and lower thirds. Suture of the two wounds in the artery, without obliterating the lumen, was considered impracticable. The common femoral artery is approximately 1½ in. (3.8 cm.) in length. A section of it, a little less than ½ in. (1.3 cm.) in length, was removed at the junction of the middle and lower thirds. The divided ends were united by an end-to-end anastomosis. The operation wound was closed except for drainage at the lower end. The tissues were relaxed by fixing the hip in a flexed position by means of a plaster-of-paris bandage.

The wound healed and the condition of the limb remained satisfactory. The popliteal and posterior pulse could be felt 24 hours after the operation. The plaster was removed at the end of three weeks, and the local condition was satisfactory when the patient was discharged from hospital four weeks after admission.

Case 2

A youth aged 19 was riding in a motor-cycle race on May 4, 1953, when his machine skidded. He was thrown off and rendered unconscious. There was a severe laceration of the left groin and bleeding was profuse. A tourniquet was applied. The accident happened at about 3.30 p.m. and he was admitted to hospital at 5 p.m.

On admission he was conscious but dazed, and general condition was satisfactory. Nothing amiss was detected with his cranial nerves. On removal of the tourniquet there was a little oozing but no severe bleeding from an irregular lacerated wound of the soft tissues in the upper third of the left thigh. The anterior and posterior pulse could not be felt; otherwise the limb was satisfactory.

Operation (6 p.m.).—The operation field in the left thigh was cleaned, and a vertical incision 6 in. (15 cm.) in length was made over the femoral artery. The common femoral artery was exposed and found to be undamaged. A clamp was applied to the femoral artery. The profunda artery was found to be intact. The superficial femoral artery was found to be torn across and there was a gap of about 1½ in. (3.8 cm.) between the divided ends, which were contracted but not bleeding. The proximal end of the divided artery just distal to the profunda was ligated. The distal end was also ligated. The wound was excised and closed except for drainage.

Progress was satisfactory, as was the condition of the limb. Five days after the injury the posterior tibial pulse was palpable. Recovery was uneventful.

J. P. Stephens, M.Chir., F.R.C.S.,
Senior Surgical Registrar.
R. M. T. Walker-Brash, B.M., B.Ch., F.R.C.S.,
Surgical Registrar.
C. Noon, F.R.C.S.,
Senior Consultant Surgeon.
Norfolk and Norwich Hospital.

Peptic Ulcer Perforation after Phenylbutazone Therapy

Among the many complications of phenylbutazone therapy, gastric ulcer activation, or formation of fresh gastric or duodenal ulcers, is well recognized. At least 15 cases of gastro-intestinal bleeding have been reported. Peptic ulcer perforation occurring during phenylbutazone therapy is rare enough to warrant the publication of the following case.

Case Report

A 53-year-old lorry driver was admitted to Surgical Department A of Frederiksberg Hospital on November 8, 1953, at 8 p.m. as an emergency case. He had been six months in a German concentration camp until the end of hostilities in 1945. There had never before been dyspeptic symptoms. He had been complaining of a slight feeling of oppression and dyspnoea on exercise for the past two years, relieved after nitroglycerin. For about a week before admission he had suffered from epigastric discomfort, heartburn, and nausea, relieved after food. Three hours before admission he was suddenly seized with acute abdominal pain in the epigastric region and under the right costal margin with no irradiation. The pain subsided without treatment. Two similar attacks occurred in the ambulance on his way to hospital and just after admission.

On examination his temperature was 37.5° C. and pulse rate 60. He was sweating, but showed no signs of dehydration. There was some fixation of the abdomen during respiration, with tenderness and muscular guarding on palpation under the right costal margin, falling off towards the right iliac fossa. Liver dullness was normal on percussion. A preliminary diagnosis of penetrating ulcer or cholelithiasis was made and he was kept under observation, with application of local heat.

It was then revealed that he had been taking phenylbutazone, 1 tablet (200 mg.) three times daily for the past week (a total of 4.2 g.) because of rheumatic pains in the left shoulder.

As his temperature rose and the pain grew worse, and as it was known that phenylbutazone could activate an ulcer and provoke a perforation, operation was decided upon. The abdomen was opened through a transverse epigastric incision, and yellowish fluid gushed out on opening the peritoneal cavity. After mopping up, a perforation the size of the head of a pin on the first part of the duodenum came into view. It was closed and the suture line reinforced with a wisp of omentum, followed by closure of the abdomen. The post-operative course was uneventful.

Comment

Four cases of peptic ulcer perforation that occurred during phenylbutazone therapy have been published (Shields *et al.*, 1953). According to Burns *et al.* (1952), Mason (1953), and others, phenylbutazone is slowly eliminated; when treatment is discontinued, it will normally be seven to eight days before a single dose is eliminated. Cases have been described in which phenylbutazone could be demonstrated in the blood two weeks after discontinuation of treatment. Accordingly, complications may occur several

days after treatment is stopped. In one case perforation actually occurred 72 hours after stopping phenylbutazone medication (Shields *et al.*). The ulcer-provoking and ulcer-activating effect of phenylbutazone has been compared with that of cortisone. Some authors have postulated that phenylbutazone acts via an adrenal cortex stimulation (Wilhelmi, 1949), but most investigators deny this (Bach, 1952; Currie, 1953; Cudkowicz and Jacobs, 1953; Domenjos, 1953).

Phenylbutazone is a dangerous drug. If it is used it should be administered, after meals, with milk or alkali. It is absolutely contraindicated in patients with peptic ulceration.

ERIK CHRISTENSEN, M.B., B.S.,
Surgical Department A, Frederiksberg Hospital, Copenhagen.

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A Fatality Due to the Use of Gold

Until the recent introduction of cortisone, A.C.T.H., and phenylbutazone, the most important drugs available for the treatment of rheumatoid arthritis were the gold salts. They are still widely used, and will continue to be, until the supply and the efficiency of the newer drugs are more satisfactory than at present. The toxic effects of gold salts are well recognized, and yet are generally supposed to be controlled if a careful watch is kept for their early manifestations, and if a certain maximum dose is not exceeded. In the present case an unusually small total dose resulted in fatal damage to the bone marrow, and the first signs of serious toxic effects developed a fortnight after the course of gold had been finished.

CASE REPORT

A married woman aged 27 was admitted to hospital on August 20 on account of menorrhagia. Her menstrual period had begun two days before admission, and she had since suffered from a continuous and very heavy loss. She gave a history of a chronic arthritis which had first shown itself immediately after the birth of her second child two and a half years before. The disease had developed very rapidly and had reached its height only nine weeks after her confinement, remaining thereafter almost stationary. It mainly affected her hands and feet, although her elbows were also involved to some extent. She had been under treatment—as an out-patient at another hospital—since the beginning, and various treatments had been tried: ascorbic acid and deoxycortone acetate, pregnenolone, and insulin. All had produced an initial improvement followed by a relapse. The first and only course of gold was begun in the middle of May.

The preparation used was "myocrisin"; the initial dose was 0.01 g. Subsequent doses at weekly intervals were 0.02, 0.03, 0.03, 0.04, and 0.05 g. This last dose was repeated four times, making a total of 0.38 g. in ten weeks. The course was finished at the end of July, and throughout it there were no toxic signs or symptoms, except a slight pruritus following the third injection. The urine was regularly tested for albumin, and the test was as regularly negative. She was seen again as an out-patient on August 10, and at that time mentioned some bruising she had on her arms. Ten days later she came into hospital.

On examination she was still losing heavily per vaginam, and in addition there were many fresh bruises and purpuric spots on her limbs, and some bleeding from the gum margins. A blood count showed: haemoglobin, 48%; white cells 3,200 per c.mm. (48% polymorphonuclears); blood platelets 2,000 per c.mm.

A transfusion of 2 pints (1,140 ml.) of fresh blood was given, raising the haemoglobin to 68%, stopping the bleeding from the gums, and diminishing the loss per vaginam.

It was considered an unlikely coincidence that she should develop an idiopathic thrombocytopenic purpura so soon after the administration of a drug known to have toxic effects on the bone marrow, and the illness was assumed to be due to gold poisoning. Two further facts supported this assumption: first, the examination of the peripheral blood (and later of the bone marrow) showed that all cellular blood elements had been affected, not only the platelets; and, secondly, the only drug that the patient had taken, apart from the gold, was aspirin—one which, although it may prolong the bleeding-time when taken in excessive doses, has never been shown to have any poisonous effect on the bone marrow. An attempt was therefore made to increase the excretion of the gold remaining in the body by using dimercaprol. A first injection of 400 mg. was given on the day after admission, and the drug was continued in a decreasing dosage for five days thereafter. The urine was tested for gold on the third and fifth days of this treatment, but none was found; and no evidence was ever obtained that dimercaprol had any effect, either at this time or when a second course was given between August 29 and September 2.

In addition to the dimercaprol and the blood transfusions she was given A.C.T.H. in a dose of 25 mg. six-hourly between August 25 and September 2. The object in giving her the hormone was only in part to relieve her arthritis, although this was achieved within the first three days of treatment, and her hands continued to improve throughout the course; it was also hoped that the A.C.T.H. might have a stimulating effect on the bone marrow. In the three or four days immediately following the first administration of A.C.T.H. there was some increase in the number of lymphocytes in the peripheral blood, but the number of polymorphonuclears showed a steady decline until the end. In view of this severe and increasing granulopenia, penicillin was given as a prophylactic measure throughout.

The patient was also given pentnucleotide, but there was no noticeable effect in the peripheral blood consequent upon it. In spite of blood transfusions she died on September 4.

At necropsy an enormous intraperitoneal haemorrhage was found which had originated from a normal ruptured ovarian follicle. This had obviously been the final event which caused her death, although haemorrhages were also present in the pelvis of the left kidney, in both pleural cavities, on the pericardium, and on the surface of the brain. Histological examination of the femoral marrow revealed merely a fatty marrow with scanty haemopoiesis, and that mainly erythroblastic.

A report on the sternal marrow, a sample of which was taken and examined on August 22, stated: "A few flecks of a very hypoplastic marrow were obtained. No megakaryocytes were seen. Erythropoiesis is normoblastic, but there is hypoplasia of the erythropoietic and myeloid tissue. There is no maturation arrest of the myeloid tissue."

Reviewing this case after an interval of time, it seems that two failures contributed to the outcome: (1) failure to appreciate the significance of the evanescent pruritus after the third injection of gold; and (2) a failure to foresee the possible danger from ovulation, which could readily have been avoided by timely administration of oestrogen.

Mild toxic symptoms of intolerance to gold occur in nearly half the patients to whom the salts are given, but it must always be remembered that these mild reactions may be the only warnings of more severe ones to come. In regard to the second failure, if ovulation had been suppressed artificially death would have been delayed at least some days, though whether this would have affected the final outcome can never be known.

I should like to thank Dr. A. L. Jacobs for permission to publish this case and for his advice during the writing of this report.

R. B. PROWSE, M.B., B.Chir.

Reviews

A STUDENT'S ANATOMY

Basic Anatomy. By G. A. G. Mitchell, O.B.E., T.D., M.B., Ch.M., D.Sc., and E. L. Patterson, M.D., Ch.B., B.Sc. (Pp. 438+viii; 286 figures. 45s.) London and Edinburgh: E. and S. Livingstone Ltd. 1954.

This book forms the basis of the introductory course given to medical and dental students in the Department of Anatomy in the University of Manchester. Its aims are: (1) to present basic facts of anatomy; (2) to give an account of how man has evolved and developed and how various tissues are arranged; and (3) to epitomize the main facts about the systems of the body. There can be no doubt that the authors have accomplished their first and second objectives. It is doubtful, however, whether a student at the beginning of his study of anatomy will gain more than a theoretical knowledge of the different organ systems unless at the same time he is either studying the systems with "dissected parts" or carrying out a general "preliminary" dissection of the whole body. The opening chapter gives a concise account of the history of anatomy and should be read and appreciated by every student. Other introductory chapters deal with prenatal and postnatal development, animal cells and tissues, and the skin. There then follow chapters on the different systems. In many instances the authors have rightly ventured beyond the traditional anatomical limits to illustrate essentials in anatomy.

The illustrations, many in colour, are numerous and well chosen to illuminate the topic under consideration. The book is beautifully produced and a credit to publishers already noted for the excellence of their publications. Certainly in the future this volume will be regarded as among the standard introductory textbooks of anatomy.

W. J. Hamilton.

ADVANCES IN PAEDIATRICS

Recent Advances in Paediatrics. Edited by Douglas Gairdner, D.M., F.R.C.P. (Pp. 470; illustrated. 42s.) London: J. and A. Churchill Ltd. 1954.

This welcome addition to Churchill's well-known "Recent Advances" series might almost be regarded as a loose-leaf replacement for a textbook on diseases of the newborn and infants, so well is this subject covered, together with a series of monographs on such subjects as the adrenogenital syndrome, tuberculosis, metabolic disorders (with special emphasis on the value of chromatography), congenital heart diseases, cerebral palsy, and nurture and mental development.

In view of the uniformly high standard both of the contents and of the writing it would be invidious to pick out for special commendation any particular chapters. The editor is to be congratulated, not only on the two sections which he himself wrote, but also on the team of 18 contributors which he has captained.

The book is well produced, and singularly free from errors, and the illustrations and tables are clear and concise. There is much valuable information for all who practise or teach paediatrics as well as for postgraduate students intending to become paediatricians.

W. Gaisford.

METHODS OF RESEARCH

Methods in Medical Research. Volume 6. Editor in Chief J. Murray Steele, M.D. (Pp. 271+vii; illustrated. $7. 53s.) Chicago: The Year Book Publishers Inc. London: Interscience Publishers Ltd. 1954.

The latest volume in this series fully maintains the high standard set by its predecessors. It deals with four unrelated subjects. The section on the design and construction of metabolism cages is comprehensive, and includes details of cages for rats, mice, dogs, and monkeys. Of topical interest is the description of cages suitable for work with radio-isotopes. Full constructional details are given and much ingenuity in design is shown. The section on methods in environmental medical research has excellent articles on respiratory exchange, the measurement of sweating, and on energy metabolism and metabolic reference standards. The use of surface area as a reference standard for basal metabolic rate determinations is not advised, and details are given of a method of determining the lean body mass from the specific gravity of a person by Archimedes' principle. This involves weighing him in air and during complete submersion in water. The section on some methods of studying human genetics is rather short, and deals with only a few special aspects of the subject. The chapter on methods for establishing the genetic role is brief and clear, and discusses in some detail the genetic aspects of peptic ulcer and diabetes mellitus. The longest section—on statistics in medical research—is edited by Donald Mainland. This does not attempt to deal with statistical methods but rather to point out how and when they can usefully be applied to research problems. It is easy to follow and lays special emphasis on the use of statistics in clinical investigations. It can be strongly recommended to anyone who wishes for a simple non-mathematical approach to this most important subject.

E. J. Wayne.

ENDOCRINOLOGY FOR THE CLINICIAN

Clinical Endocrinology. By Karl E. Paschkis, M.D., Abraham E. Rakoff, M.D., and Abraham Cantarow, M.D. (Pp. 830+xii; 253 illustrations, 5 in full colour. £5 18s. 6d.) London, Toronto, Melbourne, Sydney, and Wellington: Cassell and Co. Ltd. 1954.

This is a new textbook written jointly by a physician, a gynaecological endocrinologist, and a biochemist—all three professors at Jefferson Medical College Hospital, Philadelphia. It is written for clinicians from the standpoint of endocrine physiology. It is up-to-date but not up-to-the-minute, for it gives few references to work published later than 1950, and none to that appearing after 1952. It was written in pre-triiodothyronine days. American textbooks are two years out of date on publication, just as are those by English authors. The references are predominantly American, but some of the more important English papers —such as those by F. G. Young and H. L. Sheehan—are mentioned.

The authors emphasize their scientific approach to endocrinology, and it is therefore an enhanced pleasure to find the clinical aspects of disease so admirably discussed. They debate differential diagnosis, not as academic professors to whom all things have been revealed, nor as examinees determined to omit no consideration however improbable, but as practising physicians fully aware of the difficulties of diagnosis—difficulties frequently encountered in a large experience and often surmounted. In the differential diagnosis of thyrotoxicosis, for example, neurosis, cardiac failure, myasthenia, and the menopause are adequately considered; while in the diagnosis of myxoedema the exclusion of glomerulonephritis, hypopituitarism, anaemia, and psychosis is fully discussed. In their advice on treatment the authors are orthodox, conservative, and humane. Surgery is recommended for toxic nodular goitre; toxic diffuse goitre in the young is to be treated medically, subject to reservations concisely expressed; while in the older age groups radioactive iodine is increasingly employed. The gynaecological section deserves special commendation; only the most erudite of gynaecologists and obstetricians will fail to learn something of value here.

This might be regarded as the best textbook of clinical endocrinology for the practising physician and gynaecologist were it not for another book, equally good, with the same title and the same publisher and written by A. W. Spence. The American book is the larger by more than 100 pages, this space being given to diabetes mellitus and to

gynaecology; diabetes is omitted from the English book, and gynaecology is adequately discussed in fewer pages. Both books are written from an extensive clinical experience and out of great erudition; both are finely produced and well illustrated. Curiously, the English book has adopted the good American habit of giving the titles of all references, which the American book has discarded. Those to whom the difference in price of 58s. 6d. means something will plump for Spence.

D. V. Hubble.

HYPNOTISM

Hypnotism: An Objective Study in Suggestibility. By André M. Weitzenhoffer. (Pp. 380+xvi. 48s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall Ltd. 1953.

Hypnotism is once more enjoying a wave of popularity, and the benefits and dangers attending its use (both as a rule exaggerated) flood the popular press. Weitzenhoffer avoids extremes and achieves one of his aims in writing this book—to provide a useful source of information. His concern is mainly with the experimental work carried out by psychologists to determine objectively the significance of the events studied in what he terms "the area of suggestibility phenomena." Here are critical surveys concerning the characteristics of suggestibility, the nature of hypnotic phenomena, induced age regression, suggested organic alterations, and other allied topics.

The author prefers to remain "within the experimental setting," and consequently the therapeutic application of hypnosis has been touched upon only incidentally. Nevertheless the psychiatrist will find here an imposing array of attested experiments well worth his attention. The qualities of the hypnotist *qua* hypnotist are, unfortunately, not studied. This omission may well be because of the difficulty of applying any objective test to the therapist in action. Another omission in this objective study is any comment upon the nature of objectivity.

Many demonstrations, dear to the heart of certain hypnotists, can apparently be carried out successfully without the aid of hypnosis. The "human plank" experiment, for example, in which the subject's body is thought to become rigid by the power of suggestion, can be performed with surprising ease in the absence of suggestion by almost anyone capable of simple muscle control.

Many workers, such as Bernheim, Freud, Janet, and McDougall, gave explanations of suggestibility and hypnosis. But our author finds these explanations insufficient, for reasons clearly stated. He has attempted, very tentatively, to formulate his own theory of hypnosis, which is seen as the outcome of several interacting processes. His exposition of this theory, aided by diagrams, is far from simple, but it may well be of interest to academic psychologists.

E. A. Bennet.

STERILIZATION OF DRUGS

Sterilisations-Methoden für die Pharmazeutische und Ärtzliche Praxis. By C. L. Lautenschläger and H. Schmidt. (Pp. 320+xii. 67 illustrations. D.M. 29.70). Stuttgart: George Thieme. 1954.

This book on sterilization methods in pharmaceutical and medical practice is written by authors who evidently have a greater interest in the pharmaceutical aspect of the subject. They deal at length with the four methods of preparing a sterile medicament—namely, aseptic preparation, filtration, heating in various forms, and the addition of germicides. They describe the various classes of the latter at length, discussing their mode of action and methods of testing their activity. Included in a long chapter on chemical disinfection is a section on chemotherapeutic drugs and antibiotics. The tabular attempt to present the relative activities of these drugs against various bacteria is erroneous in several particulars: the activity of aureomycin against staphylococci is not "doubtful," nor is that of terramycin against *Ps. pyocyanea* and tubercle bacilli "unknown (not tested)"; it is also untrue to say that penicillin has "no significant activity" *in vitro* against Proteus (or even *in vivo*). The directions for sterilizing all kinds of materials, including a great variety of drugs, for parenteral injection are very full. Discontinuous heating at 80° C. (Tyndallization) recurs frequently, although it is admitted earlier that "not all substrates permit spore germination." There are also sections on the sterilization of the skin, for which quaternary ammonium compounds are favoured, of instruments and syringes, on disinfection of the sick-room, and the examination of water.

This is not the whole content of the book, since the first 85 pages are on general bacteriology, and an appendix includes chronological lists of discoveries of individual micro-organisms, dyes, disinfectants, and chemotherapeutic drugs, and of landmarks in the study of infection (starting with Fracastorius in 1546), immunity and immunotherapy, microscopy, and blood transfusion. There is much other miscellaneous and mostly more technical information for which the book will be valued, such as a list of substances with melting points differing by 1 degree from 99 to 122° C. for testing temperatures attained in autoclaves. This work will also be found convenient for discovering the composition of drugs which authors in German medical journals persist in referring to only by German proprietary names.

Lawrence P. Garrod.

PSYCHOLOGY OF THE OPPRESSED

Oppression: A Study in Social and Criminal Psychology. By Tadeusz Grygier. Foreword by Hermann Mannheim. (Pp. 362+xiv; illustrated. 28s.) London: Routledge and Kegan Paul Ltd. 1954.

The exigencies of war and revolution not only provide clinical and social psychologists with opportunities for scientific research that cannot be paralleled in their civilian experience, but enable them to test the validity of hypotheses regarding mental function originally based on hospital observation or the study of peacetime social structure. Dr. Grygier, a student of social and criminal psychology, has taken full advantage of his experiences in a Soviet concentration-camp and of a later research mission to Germany, where he studied the mentality of Polish displaced persons in various camps and prisons, and has produced a book dealing with personality changes, and more specifically changes in the psychological aspect of culture, under oppression which clinical as well as social psychologists might well envy.

Using the Otis, Picture-frustration, and Thematic Apperception Tests and supplementing these with interview techniques, all of which are applied with scrupulous care and control, the author comes to the conclusions (1) that oppression tends to produce an extrapunitive attitude in the oppressed, diverting aggression to external persons and situations; (2) that it leads to psychopathy and crime; (3) that more severe degrees of oppression greatly increase the incidence of crime; and (4) that under foreign oppression the psychological aspect of culture acquires the character of a psychopathic deviation, corresponding to the Dionysian culture pattern, conflict-ridden, aggressive, extrapunitive, and lawless. To these conclusions are added a number of interesting discussions of the relations existing between oppression, neurosis, delinquency, and racial prejudice. In assessing these findings, it is of course necessary to remember that the populations investigated were the "survivors" of oppression and may therefore have constituted a special type.

Although obviously influenced by Freudian theories and principles, Dr. Grygier has kept strictly within his own terms of reference; his scientific methods are beyond reproach and his bibliographical documentation is both extensive and intensive. The book is, in short, an outstanding achievement.

Edward Glover.

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ENDOCARDIAL FIBROSIS

Recent advances have shed light upon many hitherto imperfectly understood disorders of the heart, but much remains to be learnt about the disease, or group of diseases, characterized by fibrosis of the myocardium and endocardium. In 1946 Bedford and Konstam[1] reported a series of forty cases of unexplained heart failure occurring in African troops serving in the Middle East in the last war. Their patients complained of increasing dyspnoea for weeks or months, and were found on examination to have severe congestive cardiac failure, marked enlargement of the heart, a rapid pulse, low blood pressure, and apical systolic murmurs. No cause could be found for the condition, and necropsy in 17 fatal cases showed great dilatation of the heart, subendocardial necrosis and fibrosis, endocardial fibrosis, and hypoplasia of the aorta. The coronary arteries were normal, but organized thrombi were often found in the ventricles. The cause was considered to be possibly nutritional, with the addition of a constitutional factor associated with aortic hypoplasia. These cases bear a close resemblance to those recently described in detail by Ball and his colleagues.[2] They reported twenty cases of endomyocardial fibrosis in natives of Uganda, and described a similar clinical and pathological picture, though there were certain differences. The majority of cases had evidence of mitral incompetence (or, less often, tricuspid incompetence) in addition to severe cardiac failure, while the minority presented with only congestive failure. One patient had a large pericardial effusion. All these patients had large hearts, and in those with mitral incompetence the left auricle was enlarged. The blood pressure was usually low, and the cardiogram often showed conduction defects and T wave changes indicative of myocardial damage.

Pathological examination showed moderate cardiac hypertrophy, often great dilatation, a small hydropericardium, and, invariably, patches of pearly white endocardial fibrosis, either scattered or involving most of one or both ventricles. In two cases the condition had resulted in the complete disappearance of the apex of the right ventricular cavity, leaving little but the infundibulum, almost obliterating the inflow tract, and distorting the tricuspid ring, which was grossly dilated. The clinical signs in these two patients resembled those of constrictive pericarditis—high venous pressure with poor pulsation, ascites and oedema but no dyspnoea, faint heart sounds, tachycardia, and in one case a loud third heart sound. In contrast to the other cases in the group, murmurs were absent. Mural thrombi overlying the patches of fibrosis were common. The coronary arteries were healthy, but the myocardium showed varying degrees of degeneration, although fibrosis was not extensive. There was no appreciable inflammatory reaction.

Ball and his colleagues thought that signs of mitral incompetence formed the best clinical criterion for diagnosis of the disease, the most important differential diagnosis being from rheumatic heart disease and, in cases with obliteration of the right ventricle, from tuberculous pericarditis with constriction. They found no cause for the condition: all their patients were Africans, both sexes and all age groups being affected. Elsewhere in this issue of the *Journal* Dr. W. O'Brien reports a further series of 25 cases from the Sudan, with clinical signs closely resembling those in the other series, except that mitral incompetence was not a feature. All patients were natives of the Sudan, for the most part Arabs, their ages ranging from 35 to 84 years. In two fatal cases postmortem examination showed non-obliterative endocardial fibrosis in both, with involvement of the tricuspid valve in one.

There can be little doubt that endocardial fibrosis is a common cause of cardiac failure in Africa and the Middle East, but it is not confined to natives of these regions. Gray[3] reported two cases in white men living in Nigeria, and Hughes and Smith[4] a Scottish railway porter who died of the disease. The aetiology is extremely obscure. A nutritional cause seems improbable: Bedford and Konstam's African soldiers were well nourished, and Gray's white men were presumably living on an adequate diet, as were O'Brien's Sudanese patients. Although some of the clinical features of the disease are reminiscent of the nutritional heart disease described by Gillanders,[5] his patients all had signs of malnutrition, with fatty infiltration of the liver; nor was endocardial fibrosis found at necropsy. Evidence for an infective cause is lacking, although the common finding of a positive Wassermann reaction or eosinophilia in these patients

[1] *Brit. Heart J.*, 1946, **8**, 236.
[2] *Lancet*, 1954, **1**, 1049.
[3] *Brit. Heart J.*, 1951, **13**, 387.
[4] Ibid., 1953, **15**, 450.
[5] Ibid., 1951, **13**, 177.
[6] *Dis. Chest*, 1954, **28**, 27.
[7] *Arch. Path.* (*Chicago*), 1952, **54**, 237.
[8] *Bull. Int. Ass. med. Mus.*, 1949, **30**, 15.
[9] *Pediatrics*, 1951, **7**, 651.
[10] *Amer. J. Path.*, 1950, **26**, 969.
[11] *J. Mt Sinai Hosp.*, 1953, **20**, 100.

has led to speculation about the aetiological significance of syphilis or yaws on the one hand or a parasitic infestation on the other. Gray, however, thought that the resemblance of the lesions to those of scleroderma and certain cases of disseminated lupus erythematosus, together with the eosinophilia, was suggestive of a "collagen" disorder.

Little attempt has been made to link the endomyocardial fibrosis found in adults with that which has been well recognized in infants in recent years, yet the pathological findings are strikingly similar. Halliday[6] has recently analysed thirty cases. At necropsy the endocardium was found to be diffusely thickened, and the valve margins rolled and nodular. Nearly half his patients had associated cardiovascular anomalies, usually maldevelopment of the left side of the heart. Johnson[7] found the condition in 23 of 210 congenitally malformed hearts: these anomalies usually were of a type which might produce endocardial anoxia, and he concluded that this was an important aetiological factor. The presence of associated abnormalities of the aorta recalls Bedford and Konstam's finding of aortic hypoplasia in half their cases. Craig,[8] however, in an account of 43 cases, reported that the hearts affected by endomyocardial fibroelastosis were conspicuously free from other developmental defects, but he also considered the cause to be anoxia. At the general meeting of the Association of Clinical Pathologists a fortnight ago Dr. J. F. Horley described the post-mortem findings in three typical cases, and concluded that the most likely explanation of the pathological changes in the heart was stagnation and consequent anoxia of blood in the left ventricle. Both Craig and Edmonds and Seelye[9] rejected the hypothesis of an inflammatory lesion or a "foetal endocarditis" as the cause. Prior and Wyatt[10] noted that the fibrosis had a predilection for the left side of the heart, but obliterative lesions, such as were described by Ball and his colleagues, have not been noted in infants, unless the maldevelopment of the mitral valve and left ventricle which is sometimes seen is analogous. The infants are usually normal at birth but suddenly develop dyspnoea, cyanosis, and cardiac failure, and die quickly.

Although infective, allergic, or even nutritional causes have not been ruled out, the possibility that endocardial fibrosis has a congenital basis cannot be ignored. It may be that mild degrees of the disorder present at birth progress until they give rise to symptoms in later life; or perhaps the condition is a response of the endomyocardium to injury by anoxia, which may occur at any age, although the lack of a similar type of fibrosis in patients with coronary artery diseases makes this improbable. Research into this important disorder will need to be conducted along many lines—such as a search for an infective agent, particularly a virus; inquiry into possible nutritional factors (including attempts to produce the disease in animals fed on deficient diets); and investigation of associated metabolic disorders, or stigmata suggesting a disorder of collagen elsewhere. Haemodynamic studies earlier in the disease would be of great help, and an attempt should be made to assess at necropsy the frequency and nature of milder forms of the disease in persons of all ages who have died from other causes in areas where the condition is common. Studies of myocardial metabolism, such as are being carried out by Bing,[11] might also yield important information.

RESISTANCE TO DRUGS

In this era of chemotherapy one of the central problems is the development by bacteria of resistance to drugs, including antibiotics. Failure in treatment is often accompanied by the isolation in the laboratory of drug-resistant organisms. But discrepancies between laboratory findings and clinical response are also frequent, and they cannot all be explained away as lapses in laboratory technique or in clinical judgment. Some understanding of what is meant by drug resistance has become of importance to both clinicians and laboratory workers, for chemotherapy, with all its successes, still bristles with unsolved problems.

Although half a century ago Ehrlich and others appreciated the capacity of micro-organisms to develop resistance to drugs, it was not until about fifteen years ago that the importance of drug resistance in bacterial infections became obvious, soon after the discovery of the sulphonamides. In gonorrhoea the sulphonamides, at first so successful, were soon found more and more frequently to be ineffectual, and instead of sensitive organisms sulphonamide-resistant gonococci were isolated. Further, patients who had become infected with drug-resistant gonococci failed to respond to sulphonamide treatment. Less than ten years ago it was found that the early success of streptomycin treatment in tuberculosis was only too often followed by relapse accompanied by the development of streptomycin resistance.[1 2] In recent years increasing numbers of staphylococcal

[1] *J. Amer. med. Ass.*, 1948, **138**, 584.
[2] *British Medical Journal*, 1950, **2**, 1073.
[3] Barber, M., ibid., 1947, **2**, 863.
[4] Clarke, S. K. R., *et al.*, *Lancet*, 1952, **1**, 1132.
[5] Garrod, L. P., *British Medical Journal*, 1951, **1**, 205.
[6] *The Chemical Kinetics of the Bacterial Cell*, 1946, Oxford.
[7] Demerec, M., *J. Bact.*, 1948, **56**, 63.
[8] Lederberg, J., and Lederberg, E. M., ibid., 1952, **63**, 399.
[9] *Nature, Lond.*, 1953, **171**, 541.

infections have failed to respond to penicillin, and penicillin-resistant organisms have been isolated from such infections.[3] Still more recently clinical and laboratory resistance to aureomycin, terramycin, chloramphenicol, and erythromycin has been reported.[4] It is interesting to note, however, that drug-resistance is not ubiquitous. Sulphonamide resistance has never been a serious problem with infections due to the meningococcus, so closely related biochemically to the gonococcus, nor has penicillin-resistance in infections due to β-haemolytic streptococci, pneumococci, meningococci, and gonococci. With certain drugs resistance is more likely to arise than with others; streptomycin is particularly unsatisfactory in this respect. For example, in urinary infections treated with streptomycin, highly resistant organisms have been isolated as little as 24 hours after the start of treatment, although the organisms isolated at the start were fully sensitive.[5]

The challenge of these facts has produced many theories to explain the origin of drug resistance. There are a number of possible ways by which a bacterial population could change its character in the presence of a drug. For instance, the individual organisms in a given culture might all undergo some enzymic change directly induced by the drug. Or a few drug-resistant individuals, present in small numbers in the original population before contact with the drug, might outgrow the other drug-sensitive organisms by a simple process of selection, since they alone could survive in the presence of the drug. If the original population were mixed, a drug-resistant strain could soon outgrow a sensitive strain. Again, an originally pure sensitive strain might be replaced by a resistant one by cross-infection from another source.

In many cases of drug resistance we cannot decide between these alternatives—which are not all mutually exclusive. Our knowledge about the genetic constitution of bacteria is rapidly expanding, and there is no doubt that changes apparently very similar to the mutations of higher forms of life can occur. It is generally agreed that temporary changes may be induced by the environment but that permanent drug resistance—that is, resistance which persists even in repeated subculture in the absence of the drug—is more likely to be due to the emergence of drug-resistant mutants selected in the presence of the drug than to a change induced by the drug in all the originally sensitive cells. While it may be well recognized that a race of tail-less mice cannot be bred by simply cutting off the tails of the parents, the argument cannot necessarily be carried from mice to microbes. Gross injury to the body of a bacterium might well cause permanent injury to its genetic apparatus. This view has been ably upheld by Hinshelwood,[6] who has claimed to show that many cases of drug resistance can be explained as responses to changed chemical conditions. On the other hand, there is a good deal of evidence suggesting that drug-resistant "mutants" can be detected by special methods in cultures before exposure to a drug—and the subsequent exposure merely selects them by suppressing all the sensitive organisms.[7 8]

In this controversy between what we may call the "genetic" and the "chemical" schools of thought, there are others who try to steer a middle course. They would argue that in even the purest of pure cultures of a single bacterial species it is known that different individuals vary in size, shape, staining reactions, motility, and other properties which can be directly observed. It is obvious that similar variations may occur in any one of the thousands of different properties of organisms which cannot be directly observed in individual bacteria. In studying these we have to observe the behaviour not of individual bacteria but of bacterial populations—and the presence of individuals differing greatly from the average will be detected only if special media are employed which selectively favour their growth, as for example the selection of drug-resistant organisms in the presence of a drug. Yudkin,[9] among others, has put forward this view. He thinks that this "clonal variation" may account for many examples of drug resistance which do not seem to have the permanence or the rarity which might be expected from genuine mutations.

These academic arguments, though often inconclusive, have a close bearing on practical problems. If drug resistance is an induced change, and if induced changes are only temporary, then there is always the hope that drug-resistant organisms isolated from a patient during a course of treatment may disappear when treatment is stopped. If drug resistance is due to the emergence of resistant "mutants," then unless these mutants are very unstable, and rapidly revert back to the drug-sensitive state, resistance is more likely to persist even when the drug is stopped. New facts about bacterial resistance to drugs are still being accumulated with bewildering speed, and it is not easy to see the wood for the trees or to discern any clear general principles. Each new drug seems to pose a new set of problems and to reveal new mechanisms by which drug resistance can arise. In some cases it seems possible that, if drug resistance is a "dynamic equilibrium" so unstable as to be easily upset by quite small changes in cultural conditions, then routine sensitivity tests become meaningless or even misleading.

LATE EFFECTS OF SYPHILIS

The incidence of known new cases of early syphilis in England and Wales fell progressively from 1931 to 1940; it tended to rise in 1941 and reached its peak in 1946, after which it fell rapidly to a low figure in 1952. Similarly, reported cases of congenital syphilis steadily declined from 1931 to 1952, though there was a slight rise in the period 1942–4. This is very satisfactory, but the reduction of late and latent syphilis is much less so. Whereas the fall in early syphilis from 1951 to 1952 was in the region of 40%, that for late and latent forms was almost negligible. In fact the figures for neurosyphilis in males actually rose slightly. A suggested explanation of this is that many of these patients had undetected syphilis during the war years. If this is correct the outlook is none too rosy, for it is well known that late syphilis may not manifest itself for anything up to twenty years. In the U.S.A. also there has been no great reduction in late syphilis.

An important difference between early and late syphilis is that the patient with the former is likely to go to a public V.D. clinic, whereas a large number of those with late syphilis go to their family doctors or are to be found in the wards of general hospitals. A report on eight cases of Charcot's disease of the spine by Campbell and Boyle[1] which appeared recently in this *Journal* is a warning that this condition is less rare than may have been thought and that persistent shooting pains in tabes call for *x*-ray examination of the spine, damage to which otherwise may easily be missed. No doubt much late syphilis is never diagnosed at all as such, so that the real incidence is probably considerably greater than is generally supposed. The most incalculable form of late syphilis is the latent variety; as its name implies, this shows no physical signs and is only discovered by history and blood tests. Without routine blood tests on all patients attending hospitals and on all expectant mothers, the amount of undetected syphilis in this country will never be known.

Reported cases of congenital syphilis in the first year of life fell from 339 in 1931 to 156 in 1951 and to 110 in 1952, but later cases (in the 1–5 age group) actually rose from 89 in 1951 to 101 in 1952, while the number of cases in children from 5–15 years of age remained about the same in both years. This form of syphilis is the most easily preventable, but, as Morton[2] has recently shown in this *Journal*, it is still very much with us. The figures suggest that antenatal care is not yet perfect and that many pregnant women still have no blood tests. If such tests were invariably carried out many children would be saved from invalidity and misery every year—interstitial keratitis, for example, is easily prevented but almost impossible to cure. Routine blood testing of large numbers of persons brings problems in its train. Biological false positive reactions are not so very rare, particularly where standards of testing are not of the highest. The problem posed by the interpretation of those reactions can probably best be solved by the treponemal immobilization test, but this is as yet not generally applicable or available in this country. An interesting sidelight on this matter comes from the U.S.A., where it has been suggested that a strongly positive false biological reaction often indicates serious latent disease other than syphilis.

The fact that early syphilitic infections are steadily declining whereas late syphilis is not doing so to anything like the same extent may be explained partly by the great increase in early syphilis in 1946. About this time penicillin was coming into general use, and there is no doubt that as a result early syphilis was rendered non-contagious and apparently cured much more quickly than with the older remedies; thus early syphilis naturally showed a more rapid fall than the late forms. But though early syphilis seems to be cured by penicillin, it will be necessary to wait another ten years before we can be sure that neurosyphilis and other late manifestations will not raise their ugly heads. No great increase in late syphilis occurred after the first world war, and we may hope and expect that the same will be true after the second, more particularly because the treatment of V.D. in the armed Services was mainly in the hands of erstwhile skilled civilian specialists. Though syphilis is not the scourge it was, a good knowledge of its protean manifestations, a general awareness of the disease, and an increase in blood testing will help to ensure that treatment is always given in a stage where it is most effective.

[1] *British Medical Journal*, 1954, **1**, 1018.
[2] Ibid., 1954, **1**, 1470.

TEST MEALS

Avery Jones[1] has stated recently: "The standard test meal is, in practice, full of pitfalls and fallacies, and unless carried out with care by an interested observer will not justify the discomfort caused to the patient or the time taken in the laboratory." What the test measures—and this is not always appreciated—is the concentration of acid, which depends on the amount of acid secreted and on the rate of gastric emptying; both factors are influenced by the state of mind of the subject. Hyperchlorhydria is seldom diagnostic, but may assist the surgeon in planning the extent of gastrectomy. Achlorhydria is common in patients with hypochromic anaemia and gastric cancer; it is invariable in pernicious anaemia. But many normal subjects exhibit apparent achlorhydria, and the incidence increases with age. Bennett and Ryle[2] laid down the limits of gastric acidity for 80% of healthy medical students in response to a gruel test meal in a classic paper published in 1921, and this has been adopted as a reference by most subsequent workers using a variety of test substances. Enticknap and Merivale[3] have now extended these observations to include 95% of healthy subjects. They have also examined statistically the results in 1,000 gruel test meals, and their findings strengthen the view that the test is rarely helpful.

[1] *British Medical Journal*, 1954, **1**, 1315.
[2] *Guy's Hosp. Rep.*, 1921, **71**, 286.
[3] Ibid., 1954, **103**, 35.
[4] *Med. Clin. N. Amer.*, 1951, **35**, 593.
[5] *Gastroenterology*, 1950, **16**, 380.
[6] *J. clin. Path.*, 1953, **6**, 178.
[7] *British Medical Journal*, 1953, **2**, 1019.

As much information could be obtained with less distress to the patient by an indirect method which did not involve aspiration of gastric contents. Segal[4,5] in America has devised an elegant test which depends on the ability of hydrogen ions at a *p*H of 4 or less (that of normal gastric juice) to displace the quininium cation from a quininium-resin indicator ("diagnex"). The quinine formed is rapidly absorbed from the small intestine and is excreted in the urine, where it can be estimated quantitatively by its fluorescence in ultra-violet light. Careful preparation of the patient is essential, and the technique is fully described in recent reports by Harkness and Durant[6] and Conway and Meikle[7] in Britain. Against the ease of carrying out the test must be placed certain minor disadvantages. No substance containing aluminium, bismuth, barium, calcium, magnesium, kaolin, iron, or vitamins should have been administered for at least two days beforehand, because these ions compete with hydrogen for the resin. Since the test depends on accurate urine collection the patient should be able to empty his bladder when required, and renal function must be adequate. Finally, the test cannot indicate the absolute amounts of free acid present. Nevertheless, as a guide to the presence or absence of hydrochloric acid it is remarkably free from failures. A urinary excretion of quinine above 30 μg. in two hours indicates free acid, while a level below 20 μg., even after histamine, suggests achlorhydria (the excretion of small amounts of quinine is due to the presence of sodium, potassium, and other ions). It is obviously a useful and simple screening test, and the use of a Ryle's tube for the investigation of gastric acidity may now safely be left to the rare occasions on which it is desirable to examine a sample of gastric juice.

ANTIOXIDANTS IN FOOD

Among the penalties of urban life is the difficulty of obtaining fresh food. When storage over long periods becomes necessary the need for chemical preservatives may arise. Among substances that deteriorate on storage are edible fats and oils of all kinds, both in bulk or when incorporated into food. When stored, fat undergoes a series of chemical changes involving the uptake of oxygen and the formation of "peroxides." When the latter reach a certain concentration in the fat further chemical changes, the nature of which are little understood, lead to the appearance of volatile decomposition products. These have the flavour everyone recognizes as that of rancidity. The Food Standards Committee of the Ministry of Food has just issued a report[1] which accepts proposals made by the catering trade that certain chemicals known as antioxidants should be permitted in fat used for human consumption. The report points out that much may be done to delay the development of rancidity by proper handling and processing of the fat. The importance of this recommendation cannot be overemphasized. Thirty years ago a committee of the Ministry of Health suggested the exclusion from food of almost all preservatives designed to prevent bacterial decomposition. Trade interests protested that it might become impossible to produce many foods without them. The committee adhered to their decision, and, deprived of their reliance on chemical preservatives, the food manufacturers so improved their techniques that in many foods preservatives became unnecessary.

The present report accepts the fact that improvement in technique may not always be enough, and, where it fails, antioxidants may delay the onset of rancidity. It also makes clear that "delay" is the operative word: antioxidants cannot be used to mask rancidity once it has appeared or to render spoilt fat edible. The Food Standards Committee, having examined the scientific evidence, believe that the substances propyl, octyl, and dodecyl gallate and butylated hydroxy anisole can safely be permitted in fats used for food. The suggested concentrations are laid down and are in conformity with those in force in Canada and the U.S.A. Analytical methods capable of detecting the materials in food are said to be available. No mention is made of any possible breakdown products which presumably must occur before the antioxidants finally cease to be effective.

While the committee's views on the innocuity of these compounds from the toxicological point of view may be acceptable, some of the arguments put forward for their inclusion in food have disturbing implications. The following paragraph may be cited:

> "In the bakery trade important changes are proceeding. In some sections of the industry the preparation of baked foods is now largely concentrated in a few central factories from which distribution is made over wide areas, and thus the period between manufacture and retail sale is considerably increased. To facilitate handling it is now the accepted practice to store bulk fat at the central factories in the liquid state at temperatures a few degrees above the melting point, a condition favourable to oxidative deterioration. During the transportation and storage of products such as cakes and biscuits the 'oiling-out' of the fat on to the wrappers favours the development of rancidity."

At present no antioxidants are used in food manufactured in this country, but some may be present in imported fats. No antioxidant known at present is suitable for preserving margarine, though a need for one exists. Cooking fats and lard do not deteriorate quickly in store, nor are antioxidants needed in bulk stores of vegetable oils and fats. Animal fat and fish oils present a problem, but its magnitude is not stated in the report. The only case made for the use of these antioxidants seems to rest on their ability to preserve the "shelf-life" of confectionery, pudding mixes, and bakery products. This probably means that the mass-produced article of the big manufacturer will benefit in the competition with the products of the "little man" which are baked and sold within 48 hours or less. The committee draws attention to the toxic properties of rancid fat, but this can scarcely be a hazard for any but those with strongly perverted tastes. Antioxidants may be necessary and valuable in the national economy as preservers of fat stocks, but, if so, the report fails entirely to make out a case for their use on such grounds.

[1] "Food Standards Committee Report on Antioxidants—Revised Recommendations Relating to the Use of Antioxidants in Food," 1954, H.M.S.O. London.

TREATMENT OF CEREBRAL PALSY

[From a Special Correspondent]

As already noted briefly in the *Journal* (October 2, p. 819), the British Council for the Welfare of Spastics held a three-day conference on the treatment of cerebral palsy at B.M.A. House on September 28, 29, and 30. The conference was under the presidency of Professor N. B. Capon, professor of child health at Liverpool, and among the speakers were distinguished physicians from the United States.

In Britain cerebral palsy affects approximately 1 to 2 per 1,000 schoolchildren under 16 years of age, and there are about 6½ million children of school age in these islands. No complete survey of the age group from 0 to 5 years has yet been made, but small samples suggest that the incidence of some degree of cerebral palsy is about 0.5 to 1 per 1,000 live births. The care of these children is an immense problem even now; and the extent to which it may be aggravated in the future by the steadily decreasing mortality rate amongst premature babies and those with haemolytic disease can only be conjectured. Not only must physical care be provided, but also the type of education best suited to each child's needs. At present the educational facilities for physically handicapped children lag sadly behind those provided for the blind and deaf, and many children who should be at school cannot find a place. The powers given to local education authorities under the Education Act of 1944 are still far from being used to the full.

Importance of Detailed Diagnosis

As in every other disease, effective treatment depends on early and complete diagnosis, an understanding of the aetiological factors, and an accurate assessment of the patient's requirements and potentialities. Then can follow intelligent effort by a team, drawn from many sources, in which the patient and his parents are the most important members. This was the theme of Dr. Winthrop Phelps's (Maryland, U.S.A.) opening paper at the conference, on the differential diagnosis of the cerebral palsies and its relationship to treatment and prognosis.

Dr. Phelps has the distinction of having established throughout the world the nomenclature of the various clinical types of cerebral palsy; his practical experience is vast, and he has followed up many of his patients into middle life. His views were therefore heard with great attention. He began by reminding his audience that special-sense defects might complicate the major issue of lack of motor activity. Any method, he went on, that would give the child confidence and the will to become a self-propelling unit was the method to use for that child. He described 12 types of athetosis, based on the site of the lesion in the basal ganglia, and maintained that no single procedure could be successful in every one of these distinct clinical syndromes. Neither could the same method be expected to rehabilitate both the spastic and the athetoid child. Not only must the clinical diagnosis be made as soon as possible, with early assessment of the mental potentiality, but also the neurological factors which contributed to the physical disability must be recognized early. The time at which developmental defects, anoxia or trauma, whether primary or secondary to vascular disasters, attacked the growing foetus might profoundly influence the clinical findings.

Climbing the Vertebrate Tree

Dr. Temple Fay (Philadelphia) described the part that the defensive reflexes in the mid- and hind-brain and the spinal cord can be made to play in securing relaxation of spastic muscle groups and so rendering affected limbs more accessible to training. His work is based on his own studies of decerebrate animals and of the phylogenetic development of the vertebrate nervous system. He makes use of those old, nearly submerged reflexes, which are normally dispensed with by the human infant after the 12th day of life, to teach the spastic child to co-ordinate his limbs. At first the child is placed prone and encouraged to progress along a polished surface in the amphibian manner. Later, as in the phylogenetic progression from fish to reptile, the homolateral amphibian movements give place to a crossed pattern, which is seen in the reciprocal movements of crawling in the normal infant. By making use of the upper-segmental movement pattern, the muscles involved in a movement can be developed and reflex relaxation of the spastic antagonists achieved. Dr. Temple Fay contended that it is quicker in the long run to begin by instructing cerebral palsy patients in amphibian patterns; once these have been acquired, then and then only should the complicated crossed pattern of the reptilian stage be attempted. Later still the balance and muscle power thus attained could be used for the final stage of learning to walk, but only after the child had shown that he could creep, crawl, and kneel securely.

Dr. Temple Fay later demonstrated his training methods in a film. He also gave a short exposition on the use of carbon dioxide in selected cases. The idea of this therapy is to approach the complete relaxation and cessation of movements which take place during sleep. The results in adult patients certainly gave the impression that here was something new which might produce useful results in certain types of defects and in certain age groups.

Dr. M. A. Perlstein, president of the American Academy for Cerebral Palsy, gave a sparkling contribution on the importance of treating the child both as a whole and as a child. He advised the doctor to take a complete history from the parents, using more than one interview if necessary. It was important to be able to recognize the variations from normal which should be allowed for before abnormality was diagnosed. It was good advice to study the normal child as well as the sick child. The aim of treatment was the improvement of the whole child, not only his motor defect. Every method that might help the patient must be used, but it was vital always to remember to treat him like the child he really was. Dr. Perlstein gave many examples of his catholic use of therapeutic aids, but none was more apt than his advice that a pound on the foot of the ataxic is of more use to him than a pound in his pocket. Many drugs had been tried, he continued, but the individual reaction could be discovered only by experience. Sensitivity to some drugs limited their use, while others gained in effectiveness by being made up in an alcoholic base. Each new drug must be assessed fully before it was acclaimed as benefiting neurological dysfunction, but epilepsy must be fully controlled as soon and as efficiently as possible.

Results of Hemispherectomy

A new surgical approach to the problem of the hemiplegic was described by Mr. Wylie McKissock (London), who had performed complete hemispherectomy in 35 cases during the past five years. The criteria for treatment were quite clear: hemiplegia from early infancy, associated with epilepsy uncontrollable by drugs, severe temper upsets, and a mild degree of mental retardation. Full clinical assessment must be made by the whole neurological team. Operation might be performed at any age after the first year of life. Results were reported as being good so far as the epilepsy and the temper tantrums were concerned, but the hemiplegia was unaltered except for some improvement in the degree of spasticity.

Dr. K. Bobath (London) outlined his scheme of treatment, which depends on inhibiting over-active tonic reflexes. He said that repeated tonic reactions led to deformities, and these reactions must therefore be stopped early. This was done by holding the patient in a new, correct posture (reflex inhibitory posture) until he got used to it, the new posture being maintained for a variable length of time, depending on the patient's tolerance. Following such procedures, the muscle tone would improve, he claimed, breathing and speech would be benefited, and the child would learn in time to suppress the weakened, incorrect spasms and to hold the correct postures for longer and longer at a time. Finally, the incorrect postures would

disappear and the child could then learn to perform new muscle movements. Dr. Bobath gave no clear explanation for this phenomenon, nor how the child was handled in his own home when the therapist was not present to hold him in the right posture.

Conclusion

To sum up, the consensus at the conference was that the patient with cerebral palsy should be treated as someone who has suffered local brain damage, and that the results of the damage should be remedied at the earliest possible age. Rehabilitation of the remaining undamaged brain tissue might best be effected by making the parents and patient members of the composite medical and educational therapeutic team. That home is the best environment for any child was the conviction of all the paediatric workers, but if the child's special disabilities were too great for this it should be the aim of the admitting institution to treat him first as a child and bring the happiness of the outside world to his bedside or his chair.

SIXTH INTERNATIONAL CANCER CONGRESS

SÃO PAULO, JULY 23–29

[FROM A SPECIAL CORRESPONDENT]

Questions of cancer propaganda both to the lay public and to medical practitioners had a prominent place in the programme of the Sixth International Cancer Congress, held in São Paulo, Brazil, at the end of July. The Congress was organized by the Union Internationale Contre le Cancer, and was attended by representatives from 48 countries. The British delegation, selected by the recently formed British National Committee for Cancer, consisted of Lord Horder, Dr. Cuthbert Dukes, and Professor Alexander Haddow.

Many of the subjects in the widely ranging scientific programme were dealt with as panel discussions by a team of invited speakers, a method that succeeds in canalizing discussion but carries the danger of sometimes confining it within too narrow limits.

Cancer Propaganda and the Public

Cancer propaganda was the subject of both a symposium and several sessions of proffered papers. Most speakers at the Congress appeared to accept unhesitatingly the value of lay propaganda and that an intensive campaign directed towards the lay public was an essential part of any cancer organization. Many of them described in great detail the methods employed. Undoubtedly such propaganda, if intensively conducted, will always cause considerable interest among the public and will attract voluntary donations for the fight against cancer. However, there seems to have been no clarification of the questions whether, as a result, there is an appreciable increase in cases treated at a less advanced stage, or whether harm may be done by increasing fear of the disease.

The American Cancer Society, which has had the greatest experience of this type of propaganda, still conducts its intensive campaign, but now there seems to be a somewhat different orientation and greater awareness of the possible dangers of a campaign in which fear of cancer plays a prominent part. It appears that lay propaganda is likely to produce most results in those countries which are medically less advanced and where there are large numbers of advanced, undiagnosed, and untreated cases. In countries where medical organization is on a sounder basis any dividends to be gained will probably be less and shrink rapidly with succeeding years.

Towards an International Classification

Several sessions were devoted to a study of the "Clinical Stages of Cancer" with the object of obtaining agreement on clinical classification in a variety of sites. The advantage of an internationally agreed classification of stages is that it might help to eliminate much of the confusion which now occurs when the published results of one centre are compared with those of another. A commission of the International Radiological Congress in Copenhagen in 1953 issued a report on this subject, and it is hoped that the deliberations of both congresses can be merged so that there can be true international uniformity of reporting.

The Section on Cancer Prevention naturally dealt, in one of its sessions, with that currently most important topic of smoking and cancer of the lung. The views expressed seemed to be in confirmation of some association between excessive cigarette smoking and lung cancer. Another symposium in this Section was devoted to the problem of the addition of colouring material to foodstuffs. It is a matter which has been under discussion for some time, and there are obviously conflicting views. One group suggests that there are seven substances which have been found by animal experimentation to be non-carcinogenic, and eight others which also appear likely to be non-carcinogenic should be allowed to be incorporated in foodstuffs by international agreement. The other group apparently doubts the validity of such animal experimentation and advocates the abolition of the addition of any artificial colouring matter, even though it may have become traditional by long usage.

As is usual at international congresses, the main value to the participants was not the scientific sessions, with some outstanding exceptions such as the discussion on steroid metabolism and cancer by Huggins of Chicago and Lipschutz of Santiago, but the meeting together of the workers in various fields from different countries. The setting in São Paulo was an interesting and stimulating one, particularly as this Congress was a part of the celebration of the fourth centenary of the founding of this rapidly expanding city of coffee, confidence, and concrete skyscrapers. Of some added interest was the appearance of a six-man delegation from Soviet Russia which joined the business meeting and provided a series of five papers as a late addition to the scientific programme.

MEDICAL PROTECTION SOCIETY

Presiding at the sixty-second annual general meeting of the Medical Protection Society on October 6, Sir ERNEST ROCK CARLING said that doctors, like others, were subject to aberrations, and when it appeared to them that a mistake might reasonably have been avoided they accepted the consequences; but that was very different from acceptance of the view that every mischance of treatment or operation was due to negligence. "We adhere firmly to the judicially expressed view that even with reasonable care and skill—even in the hands of the meticulously careful and most highly skilled—mishaps and unforeseeable accidents are not only possible but, in the nature of our work, now and again inevitable. That position we defend with all our might."

Ill-advised Comments in Coroners' Courts

Dealing with the undesirability of comment by coroners' pathologists in criticism of the clinical conduct of a case from post-mortem evidence, Sir Ernest Rock Carling said that proverbs were generally a sound basis for human conduct. "To be wise after the event" was not an indication of an admirable character, and when it paved the way for common-law actions against another person who had had the responsibility for a patient critically ill it was reprehensible. Difficult situations sometimes arose from the use of apparatus potentially dangerous. Which individual in theatre practice could be held responsible for the continuing perfection of a complicated piece of electrical apparatus? There might be regular dates for tests, but what if an accident happened the day before that test fell due?

Sir Ernest Rock Carling went on to say that the Society was still not entirely satisfied with the working of some of the dental service arrangements. Oddly enough, the best dentures were not necessarily more beautiful, more comfortable, or more efficient than a perfect set of natural teeth, though many people expected them to be. He reminded

dental surgeons of the importance of obtaining a written understanding from any N.H.S. patient for whom he proposed to do work not provided for in the scheme, and to complete any dental treatment under the N.H.S. before commencing further treatment of the patient privately.

Mr. W. M. MOLLISON, the treasurer, said that notwithstanding the increased prevalence of actions against hospitals and doctors the finances were in a satisfactory state. Income for the year had exceeded expenditure by £9,898. The financial resources of the Society on December 31 last exceeded £170,000. This amount included the accumulated funds (£127,288) and the amount of the members' liability. In addition, the Society was reinsured with Lloyd's underwriters for a considerable sum.

On the proposition of Dr. T. BEATON, seconded by Dr. J. MURRAY ROBERTSON, Sir ERNEST ROCK CARLING was re-elected to the presidency with much acclamation, and the other officers and retiring members of council were also re-elected unanimously. The report of the council, which was adopted at the meeting, stated that the total membership at the end of last year was 28,545, and the number of new cases in which members had sought the advice and assistance of the Society during the year was 2,020.

THE NEW ACADEMIC YEAR

UNIVERSITY COLLEGE HOSPITAL

Sir Geoffrey Vickers on the Doctor as Educator

The opening ceremony of the new session on October 5 was the occasion of the introduction of the new Dean, Mr. J. D. S. FLEW. He succeeds Dr. JOHN HAWKSLEY, who has held this office for the last five years. The Dean's report stated that the school was also losing, by retirement, Mr. JULIAN TAYLOR, who had been associated with the School, the College, and the Hospital for 50 years, giving distinguished service as surgeon and teacher.

During the year the School had acquired more houses in Gower Street for hostel accommodation, but it was the ultimate goal to build a new and well-equipped hostel of adequate size. Another major development had been the opening, the previous week, by Sir NORMAN BIRKETT, of a new sports ground, more easily accessible and also providing recreational facilities for the nursing staff which had not been available before. The report also referred to the rather disturbing difficulties that had arisen resulting in a delay in the pre-registration of certain students from Oxford and Cambridge. The Dean hoped that the two universities would be able to make similar arrangements with the General Medical Council to those existing between that body and the University of London.

After the prizes had been distributed by Lady Vickers, an address was given by Sir GEOFFREY VICKERS, V.C., a member of the National Coal Board with special responsibility for manpower, welfare and health services, and also a member of the Guillebaud Committee.

The Profession and the Public

Sir Geoffrey Vickers, who is a lawyer, said that there was a great deal that the professions of law and medicine had in common that was absent from non-professional work. The medical profession had now passed from being a private public service to being a "public public service." It was from doctors that laymen were going ultimately, directly or indirectly, to get their ideas about health and disease and health services. Education in this respect was one of their major responsibilities. In this respect—as educators—doctors were not different from every other profession, for it was always necessary to teach clients what they might and might not expect of a profession and of themselves. The relation between the professional man and the layman whom he was advising was, both in law and in medicine, a partnership—subtle, intimate, mutual. The professional man, who had the greater insight into what was needed to make that partnership work, had also the greater responsibility for seeing that it did work. In the medical profession, doctors made things a lot harder for themselves by calling their clients "patients," thereby suggesting that their part was simply to suffer.

The doctor's influence was particularly important now, continued Sir Geoffrey Vickers, when the attitude of lay people to health and disease might be sadly awry. We stood to-day at the end of a long period which had virtually seen the conquest of bacterial infection. The full implications of this conquest were as yet only dimly seen. For one thing it had altered the shape of public health and made possible urban civilization as we knew it, and had increased the expectation of life. Laymen were certainly a long way from understanding how to live in a world in which bacteria had been defeated. They had come to expect that doctors would probably preserve them from most of the hazards which half a century or so ago thinned each generation in early or middle life. But we were now tumbling to the fact that, whereas we had hoped doctors would find specific cures for this and that, probably in the majority of cases the doctor would only be able to palliate and prolong.

What laymen should be asking the doctors for was help in attaining and holding a level of health or of immunity which would keep at bay for as long as possible the disease which would ultimately kill them, and also help to bear the years of enfeeblement and degeneration.

Sir Geoffrey Vickers stressed the importance of preventive medicine, which worked from both ends—by reducing hazards and by removing the results of infection. But it still had a long way to go, and he sometimes thought it was a pity that the public health services should be administered separately from the therapeutic ones. He urged the doctors to keep as close as possible to their colleagues, medical and lay, in the public health service. Laymen as well as doctors had the responsibility of seeing that the National Health Service worked as well as possible; it was a partnership, but the doctor was the senior partner, with the responsibility of guiding the patient as well as himself.

"The practice of a profession," said Sir Geoffrey Vickers in conclusion, "is essentially the exercise of insight, that human faculty which is of all faculties the most delightful in its exercise and the most blessed in its results."

BIRMINGHAM MEDICAL SCHOOL

At the opening ceremony of the Faculty of Medicine, Birmingham University, on October 4, the chair was taken by the Dean, Professor A. P. THOMSON, who reviewed the progress of the Medical School during the previous year. There had been no decline in the standard of students accepted in the school, he said, and in view of the large number of applications for admission there was good reason to believe that this standard would be maintained. Referring to public discussions of the possibility of training too many doctors, Professor Thomson suggested that the number of alternatives open to a medical graduate was so great that at present there was little cause for anxiety. He referred to his recent experience in East Africa as a member of the Inter-University Council for Higher Education in the Colonies, and of the challenging opportunities offered in the colonies to medical graduates. Professor Thomson then introduced Sir Richard Livingstone, who presented prizes to students and delivered an address entitled "A Philosophy of Life."

A Philosophy of Life

Sir RICHARD LIVINGSTONE introduced his subject by contrasting the immense successes of science with the much less impressive achievements in the fields of private and public conduct. The difference, he suggested, might be attributable to the fact that science had a sense of direction which derived from a clear recognition of objectives, whereas in the field of morals a similar philosophy was lacking. The greatest need of the present age, he continued, was a philosophy of life, by which he meant that we should have a clear judgment of what is good and of what is bad, and

some understanding of the considerations upon which that judgment rested. There was evidence from the ancient world that it was possible to achieve such a philosophy and to live by it. During the late fifth and fourth centuries B.C. the problem confronting Greek thinkers was in many respects similar to our own—namely, the impact of a scientific view of life on accepted values. Plato asked: What is good? In what kind of State can the good life be lived? And these were questions to which we too must attempt to provide an answer. Referring to Aristotle's view of the good life as the exercise of man's highest functions, the life of reason, Sir Richard recognized both the value of this view and its limitations. Its weakness was the weakness of Greek thought: so defined, the good life could be lived only by a minority. A corrective was necessary, and could be found in the Christian view of the good life as the life of love.

Sir Richard finally referred to the need for a book on ethics which would be both modern and practical. The author of such a book would have to take the Aristotelian approach, and until the book was written we could usefully turn once again to Aristotle. He had at least asked the pertinent questions, and his emphasis on the use of reason pointed to a philosophy. Without such a philosophy we should find that:

> "The centre cannot hold; things fall apart.
> Mere anarchy is loosed upon the world."

WESTMINSTER MEDICAL SCHOOL

Address by Master of Balliol

The inaugural ceremony at Westminster Medical School took place at Church House, Westminster, on October 4. The chair was taken by Mr. H. M. Clowes, chairman of the School Council, and an address was delivered by Sir David Lindsay-Keir, Master of Balliol.

Sir David Lindsay-Keir said that he happened to be chairman of governors of the most recently established teaching hospital in the kingdom. They in Oxford had long been accustomed to the teaching of preclinical subjects; moreover, in more recent years they had through the munificence of Lord Nuffield the opportunity of becoming associated with the advancement of medical research. But in the teaching of clinical medicine they were still beginners, and it was very heartening to him that day to be associated with the traditions established by one of the great hospitals and medical schools of London.

He proceeded to speak of the conquests of medicine during the last two hundred years—during, in fact, the history of Westminster Hospital—particularly in the field of tropical medicine. For many centuries in large parts of the world human development and sometimes the very possibility of human life had been restricted, halted, driven into retreat by environmental factors which man had been unable to influence or to control. During the last 200 years there had arisen an entirely new situation. Man was no longer on the defensive. Armed with the discoveries of medical science, a revolution in human affairs had come about for which western medicine was primarily responsible. But even more important than the knowledge, the technology, and the equipment which western medicine had brought to the elimination of disease was the dedication, the wisdom, the character, the sympathy of the men and women who, trained in their art, had brought the benefits of medicine to the masses of mankind.

The Dean, Mr. H. E. Harding, in his report, said that the Academic Board would shortly have before it the question of the development policy for the next quinquennium. Plans for the clinical departments had had to be altered for lack of space. In the department of pathology alone had building development been possible. A new pathology department had been built in Vincent Square which would also provide routine pathological services for the Children's and the Gordon Hospitals. The purchase of 28 acres of land in Surrey—15 acres of which were now in full use—had given the School admirable playing-fields.

Reports of Societies

MIDLAND MEDICAL SOCIETY CENTENARY

On October 13 the Midland Medical Society, one of the oldest medical societies in the country, celebrated the centenary of the election of its first president, Dr. James Johnstone, who assumed office in 1854. Dr. Johnstone was the son of Dr. Edward Johnstone, the first president of the Provincial Medical Association at Worcester, the forerunner of the B.M.A., and was himself elected to the presidency of the Association in 1856, when it assumed its present name. The Midland Medical Society's celebration took the form of a dinner at the Grand Hotel, Birmingham, which was attended by representatives of the City, the Church, the Law, and the University.

[*Birmingham Post and Mail*

The origins of the Society appear to go back to 1841, when a group of local doctors formed the Queen's College Debating Society with the avowed object of advancing the knowledge of medicine and surgery. Later the name of the Society was changed to the Midland Medical Society. The history of the early days has been recorded by Professor A. P. Thomson, dean of the medical faculty at Birmingham, in an article published 30 years ago in the *Midland Medical Journal*, when Dr. Thomson, as he then was, was the Society's honorary secretary. The Society had difficulty in finding a permanent abode: it met at various times at Queen's College, in a room at the Birmingham Library, and at the Midland Institute, until in 1880 it finally settled at the Birmingham Medical Institute, its present headquarters.

In 1868 there was a crisis in the Society's affairs. Some members wished to open negotiations with the B.M.A. with a view to amalgamation. Opinions were sharply divided, but after a series of heated discussions the opponents of amalgamation won the day and the Society retained its identity. One of the notable features of the Society has been the long list of distinguished guest speakers who have delivered the inaugural address at each session. The list goes back unbroken, except for the two world wars, to 1870. Among the famous names are Lister, Jenner, Clifford Allbutt, Spencer Wells, Sidney Ringer, and Victor Horsley.

To-day, the Midland Medical Society under its president, Professor H. F. Humphreys, the Vice-Chancellor of Birmingham University, is as active as ever. It meets fortnightly, when the programme may be a clinical session or a lecture by a well-known medical man. To mark the centenary a presidential badge has been made, and is here illustrated. It is devised in four colours of gold, and incorporates, with the traditional rod and serpent of Aesculapius, two sprays of the foxglove in honour of Dr. William Withering, the eighteenth-century Midland medical practitioner who first applied digitalis to the treatment of heart disease.

Correspondence

Smoking and Lung Cancer

Sir,—The suggestion is made severally by Drs. H. Stalker and P. Glees (*Journal*, September 18, p. 702) that the wasteful habits in smoking by some Americans may make the official figures of tobacco consumption misleading; this may be the case, but it would need another investigation to assess the degree. In your issue of October 2 (p. 808) Dr. Richard Doll and Professor A. Bradford Hill take exception to my logic and arithmetic. I wonder whether your readers prefer this sample of Dr. Doll's arithmetic: "One single cigarette holds the risk of lung cancer. Take two and the risk is doubled." I commented unfavourably on his statement: "Even very heavy smoking does not appear to be uniformly carcinogenic"; instead of trying to justify the statement, a diversion is made into hypothetical statistics of influenza. There were six observational points on a graph to which I took exception. An experimentalist would plot the points, join them up, and inspect them; the most casual inspection would show that these six points did not lie on a straight line. The statisticians, however, knew the "best-fitting line" through them and obtained a correlation coefficient 0.62 regarding which they say: "We are not ourselves enamoured of correlation coefficients based upon six observations, but, in fact, the figure is 0.62; for what it is worth, then, these observations are associated to quite a high degree." Four months ago I asked a statistician to give me his opinion on this particular coefficient, and I quote from his letter: "The data thus hardly warrant the assumption of any linear relation. It is clear that the two values for high cigarette consumption spoil the chances of correlation."

The matter may be looked at in another way. The lung cancer death rate for England and Wales reads 280 per million *actually*; on the best-fitting line it reads 170, a figure 39% too low. The rate for U.S.A. reads 120 per million *actually*; on the best-fitting line it reads 210, a figure 75% too high. I think that a false picture is presented by drawing a straight line through such points and then claiming that the result "is not inconsistent with the existence of a relationship between lung cancer and cigarette smoking."—I am, etc.,

London, W.C.1. Sidney Russ.

The M'Naghten Rules

Sir,—In the matter of Dr. Eliot Slater's article on the M'Naghten Rules (*Journal*, September 25, p. 713) I would beg leave to occupy a little of your space for the purpose of making some general observations. "Now if every act which a man performs," says Dr. Slater, "is determined by his own nature on the one side and circumstances on the other, then no other way of acting was open to him." Behold, gentle reader, open your mouth wide enough to swallow this monstrous if, and you are absolved henceforth from all responsibility in the conduct of your life. And, though you have no say in your destiny, at any rate you cannot be blamed for any of the disasters which the shortcomings of your mechanism or the exigencies of your environment cause you to bring upon your fellows. Here is an end to all anxiety, for why should you worry when the inevitable is the unique solution to your problem?

The nearest that this hypothesis approaches to credence is in childhood, whereas in adolescence and maturity the individual develops an increasing sense of responsibility as he learns to exert his will. But Dr. Slater says, "Responsibility offers extraordinary difficulties," and therefore he abandons it altogether with the concept of free will, since to consider free will would introduce "an element of the unknowable." Such self-imposed tubular vision may clarify the issue over a limited field, but one must necessarily limit the application of any conclusions to the world lying at the end of the tube. Indeed, the psychiatrists seem to have immured themselves within a secret garden to which outside sounds float only dimly and from whence we are bombarded with leaflets couched in an occult jargon. What weight should we give to pronouncements from within this pale? Should they be revered for their esoteric wisdom or reviled for their obscurity? It is difficult to tell as a rule what they mean.

But the meaning stands openly in Dr. Slater's article, and it does not incline me in his favour. He has to mutilate life overmuch before he can cram her into his scientific box, and I am reminded of the antics of Cinderella's haughty sisters in their attempts to make the shoe fit. I think Dr. Slater would do better to accept the foot which Nature has provided, put away his knife, and play a game of hunt the slipper.—I am, etc.,

Edinburgh, 12. Alan Lyell.

Sir,—Few of us who have ever given evidence in court will deny that the M'Naghten Rules need revision, even if only to make their language more easily intelligible. But Dr. Eliot Slater's exposition of determinism (*Journal*, September 25, p. 713) seems to lack consistency in parts. He says that a man's acts must be assumed to be due to "his make-up; his physical and mental state at the time; the circumstances and his appreciation of them." And: "Now if every act which a man performs is determined by his nature on one side and circumstances on the other, then no other way of acting was open to him." "The application of such concepts as responsibility, innocence, and guilt becomes nonsensical. In psychiatry we do very well without them." And in another place "'free will' proves a heuristically sterile idea."

To put it shortly, everyone acts that way because he is made that way and has to seems to be the view of the lecture. So in Straffen's case, he murders a child; he was made that way; he had to. The first court finds him insane: they were made that way: they had to. The warder was careless; he was made that way. The second court under Mr. Justice Cassels decides he is sane enough to be condemned; they were made that way and strictly interpreted the rules *inevitably* made by the M'Naghten judges a hundred years before; they had to. A story not less distressing for a doubt as to whether the second child's death was really inevitable. But the whole tone and purpose of the lecture implies that the M'Naghten judges and Mr. Justice Cassels ought to, and therefore could, have acted differently.

And it is stated further: "The judge is *free* to ignore the Rules if he so wishes" (my italics). "The judge can exercise a large measure of control on the jury's decision." The judges, therefore, have choice of more than one course of action under the same circumstances. See also the paragraph on Scandinavian practice. Is it fair to say, then, that the judge has free will and the criminal none? Is, then, the judge the sole exception to the rule of determinism, or does free will only occur above a certain intellectual level? (I would not be sure myself that my dog has no free will.) Or is free will treated as we used to deal with friction in elementary mechanics, and left out as too difficult?

Sir, my only excuse for this letter is that I am made that way: I had to.—I am, etc.,

King's Langley. Reginald Fisher.

Primidone in the Treatment of Epilepsy

Sir,—We were interested in the articles on primidone in the treatment of epilepsy by Drs. J. B. Lyons and L. A. Liversedge, and Dr. D. S. Sharpe (*Journal*, September 11, p. 625, and p. 627 respectively), particularly as we were preparing a paper concerning the use of the drug in mental deficiency practice. As our series is small, however, and as we have little to add to what has already been published, we have decided not to proceed, though we should be grateful for the opportunity to record a brief summary of our findings.

"Mysoline" was given to 17 patients whose fits had not been controlled by any other drug or combination of drugs,

with the following results: complete control, 2; improved, 9; no change, 1; worse, 3; died in status epilepticus, 2.

We agree that the drug is a valuable anticonvulsant agent, but in the light of further experience we feel that the dosage was probably inadequate in our two fatal cases and would advise increasing it to the limit of tolerance, with the addition of phenytoin sodium if necessary, as long as any fits occur.—We are, etc.,

C. Guy Millman.
Jane H. Thompson.

Morpeth.

Sexing the Unborn Foetus

Sir,—My attention has been drawn to an article which recently appeared in one of the national daily newspapers, and which states, *inter alia*, that it is possible to predict the sex of an unborn child by means of a test applied to litmus paper previously placed on the expectant mother's tongue. Such tests, it is stated, have proved accurate to the extent of 90% in Britain and of 93% in the United States. The article goes on, "If you want to know which sex your baby will be, ask your National Health doctor. He can arrange a diagnosis for a guinea. It is so easy that one firm of baby clothes makers offers the test free—and a switch of clothing if they are wrong."

I presume this test must be a modification of that described by Rapp and Richardson.[1] If it is, I know of no published confirmation of the accuracy claimed for it. On theoretical grounds, both chemical and biological, it is highly improbable that the test would work; and limited experience with it in my own laboratory led to the conclusion that it is worthless. In point of fact, it would seem that the best that can be done for sexing the unborn foetus is still no more than what one eminent obstetrician (now deceased) claimed to do: he told the expectant mother, at her first visit, that she would have a boy (or a girl), and then wrote in his book the opposite sex. If what he had said was right the parents thought him extremely clever, and if what he had said was wrong he could deny it by showing that he written down the correct sex.—I am, etc.,

G. I. M. Swyer.

London, N.W.1.

Reference
[1] *Science*, 1952, 115, 265.

West London Hospital Medical School

Sir,—We have recently heard that in the very near future there is a danger of the West London Hospital ceasing to be a teaching hospital, and this has been confirmed by the hospital and medical school authorities. In these circumstances we, who were students in either pre-, post-, or inter-war stages of the medical school, would like to register a very strong protest and at the same time to put in a plea for the continuation of its valuable instruction. From its inception in 1937 until the last full entry of undergraduates qualified in 1952, it provided its students with an excellent clinical training, despite the added difficulties of wartime.

The small size of the West London Hospital Medical School has often been cited as an adverse criticism, but we feel this was one of its great advantages. Formal lectures were intentionally few, the policy being to rely on reading, seeing, and on first-class tutorials. The firms were always small so that individual teaching at the bedside and in the out-patient department was proportionately greater. There was infinitely more opportunity for assisting at operations and for gaining experience in the casualty department. When a special department—for example, midwifery or geriatrics—was not represented at the West London this was remedied by association with neighbouring hospitals and utilization of some of their enormous reserves of teaching material. Not only did this arrangement often provide material that even the largest of teaching hospitals could not hope to concentrate in one centre, but provided that much-needed bridge between the teaching and non-teaching hospitals, both at student and staff level.

Between 1937 and 1952 230 students have qualified from the West London Hospital Medical School. Although most of these are women (the school was started on condition that it gave preference to women) and a large proportion of them are married, 79% of them are still working. They are scattered throughout all branches of hospital practice, the public health service, the public health laboratories, in research, general practice, the colonial medical service, and a few are doing missionary work. Their practical and written work since qualifying and the number of post-graduate degrees and diplomas gained by old students give some indication that the academic standard reached by them did not fall short of that obtaining in the larger schools.—We are, etc.,

Helen Wagstaff. Patricia Wallace.
Helen Mayer. Rosemary Davies.
Elizabeth Falle. Agnes Bartels.

Chingford, London, E.4.

Normal C.S.F. Sugar in Tuberculous Meningitis

Sir,—Dr. G. D. W. McKendrick (*Journal*, October 2, p. 811) stresses that the cerebrospinal fluid sugar content in tuberculous meningitis may be normal in the early stages. I have had four cases out of a series of 63 in whom the minimum finding was over 50 mg. In a female aged 36 the C.S.F. sugar was 50 mg. on admission, and nine days later, without any treatment, had risen to 86 mg. Treatment was then started without any precise indication, and she died on the fifteenth day, necropsy confirming the diagnosis. The C.S.F. sugar remained over 75 mg. MacLean[1] showed that convulsions will temporarily elevate both the blood and later the C.S.F. sugar. Valuable as this test remains, it is not infallible.—I am, etc.,

J. L. Fluker.

Plymouth.

Reference
[1] *Arch. Dis. Childh.*, 1936, 11, 247.

Sir,—I should like to make further comment on the finding of a normal C.S.F. sugar in tuberculous meningitis (Dr. J. G. Alexander, *Journal*, September 11, p. 646, and Dr. G. D. W. McKendrick, *Journal*, October 2, p. 811). My remarks are based on a two-year study carried out before the introduction of streptomycin and isoniazid. Then the outcome of the disease was inevitably fatal and changes in the C.S.F. cell picture, biochemistry, and bacteriology could be correlated with the day-to-day deterioration in clinical condition. While a normal C.S.F. sugar was occasionally found at almost any stage in the disease, a normal C.S.F.: blood sugar ratio (0.60) was rare.[1] Convulsions produce a rise in blood sugar[2] and are the most likely reason for the finding of an apparently normal C.S.F. sugar in tuberculous meningitis. It has been shown[3] that C.S.F. sugar can be raised in both normal children and in cases of tuberculous meningitis by raising the blood sugar with glucose given intravenously.

Neither Dr. Alexander nor Dr. McKendrick mention whether any of their cases with normal C.S.F. sugar suffered from convulsions previous to lumbar puncture. In my experience, the convulsion was frequently the first symptom which drew the parents' attention to the illness, and generally preceded the child's arrival in hospital by an hour or more—sufficient time for the increase in circulating blood sugar to have its effect on the C.S.F. Lymphocytes are not actively glycolytic. Polymorphs possess considerable powers of glycolysis and, as they predominate in the C.S.F. towards the later stages of the disease, the tendency is for the C.S.F. sugar level to become lower as their numbers increase. It is possible, under the present methods of treatment, plus perhaps earlier diagnosis, that the disease is often arrested before this stage is reached.—I am, etc.,

Esther Hendry Welbourn.

Cambridge.

References
[1] Hendry, E. (1939). *Arch. Dis. Childh.*, 14, 159.
[2] Maclean, M. B. (1936). Ibid., 11, 247.
[3] Hendry, E. (1939). Ibid., 14, 307.

Diabetes as the First Sign of Pancreatic Carcinoma

Sir,—Dr. R. D. Lawrence's statement (*Journal*, September 4, p. 593) that diabetes mellitus is rarely the *first* sign of pancreatic carcinoma should not be allowed to obscure the fact that abnormal carbohydrate metabolism is a common feature of this disease, although this does not appear

to be widely known in this country. Dashiell and Palmer[1] refer to 920 cases culled from the literature, of whom no fewer than 108 had glycosuria; of their own cases of carcinoma of the pancreas, 18 out of the 21 tested had abnormal dextrose-tolerance curves. Arkin and his colleagues[2] state that in general 50% of cases of pancreatic carcinoma may be expected to have abnormal glucose tolerance and 10% to have diabetes; in their own series of 75 cases, one-quarter had diminished tolerance. Brown *et al.*[3] observed glycosuria in 20 (2 of whom were definitely diabetic) out of 100 cases, and Burke and Plummer[4] subjected 15 of their 30 cases to a glucose-tolerance test, and obtained abnormal results in seven.

In Britain we do not seem to be aware of the value of this investigation in this regard. A scrutiny of the *Cumulative Index Medicus* and the *List of Current Medical Literature* from 1949 to 1953 did not reveal a publication on this subject in a British journal, although the British authors Strang and Walton[5] refer to the subject very briefly in an article in an American journal. Suspecting that perhaps pancreatic carcinoma might behave differently in Britain, I inspected the case notes of all the cases of this disease registered in the cancer files of St. Bartholomew's Hospital between mid-1947 (when registration began) and December, 1953. The results were as follows: total number of cases, 70; number with heavy glycosuria ("red" to Benedict's), 12. Ten out of these 12 were subjected to the glucose-tolerance test and all had diabetic curves. One of the twelve had been a known diabetic for 18 years and one for two years. In addition to these 12, there were a further three whose urine always reduced Benedict's reagent to green, and a further 15 who had traces of unidentified reducing substances in the urine from time to time.

Thus the pancreatic carcinomas at St. Bartholomew's Hospital seem to have followed the pattern described in the American literature, with an incidence of diabetes of about 20%. How many of these diabetics would have had their cancers diagnosed at a curable stage if a glucose-tolerance test had been carried out earlier in their illness we cannot guess; nor is it fruitful to speculate in the present state of our knowledge what the findings might have been (or what therapeutic action might have been taken) if glucose tolerance tests had been performed on each of the 70. What does emerge is the necessity for a long-term investigation, in a centre which deals with reasonably large numbers of this fairly uncommon disease, of carbohydrate metabolism in relation to carcinoma of the pancreas.—I am, etc.,

London, E.C.1. IAIN MACDOUGALL.

REFERENCES

[1] *Arch. intern. Med.*, 1948, **81**, 173.
[2] *Gastroenterology*, 1949, **13**, 118.
[3] *Amer. J. med. Sci.*, 1952, **223**, 349.
[4] *Va med. Mon.*, 1953, **80**, 333.
[5] *Ann. intern. Med.*, 1953, **39**, 15.

St. John's Hospital, Lewisham

SIR,—May I, as a very minor historian of Medicine, be permitted to support the letter from Mr. H. P. Winsbury-White (*Journal*, October 2, p. 811)? The relegation of St. John's Hospital, Lewisham, to the status of a specialized hospital, with the consequent disappearance or diminution of its nurses' training school, would be nothing short of a tragedy.

In the year 1848, a number of doctors of King's College Hospital, including Bentley Todd, William Bowman, and Lionel Beale, became dissatisfied with the "Gamp" system of nursing, and they therefore founded, at St. John's House, Queen's Square, Westminster, a training institution for nurses on a definitely religious basis. The lady superintendent, the seven honorary lady sisters, and the 35 paid nurses were taught to regard their work "as a holy function; not as a mere trade, but as a dignified office." In 1853 Miss Florence Nightingale was invited to organize a training school upon the same lines at King's. The Crimean war intervened, and Miss Nightingale thought it her duty to organize the nursing of the wounded; to assist her, she took a number of the nurses of St. John's House. In 1856, after the war was over, the entire nursing of King's and Charing Cross Hospitals was undertaken by St. John's. In 1885 the association between St. John's and King's came to an end. The nursing sisters founded their own hospital, and, after various vicissitudes, found a permanent home at Morden Hill, Blackheath, under the name of St. John's Hospital, Lewisham. Thus the nurses' training school of St. John's Hospital, Lewisham, is the direct descendant, in an unbroken line, of the pre-Nightingale training school, St. John's House.

There is at present a movement on foot to preserve, at an enormous cost, a few insignificant remains of a pagan temple in the City of London. It is no dead stone, but a living entity, which we hope to preserve at St. John's. The regional board states that it would not be necessary to close the training school at St. John's, but that the nurses could go to other hospitals for much of their training. It is obvious that the individuality of St. John's would perish if such a scheme is implemented. I hope very much that the few remaining members of the pre-nationalization staff of St. John's will not be left to fight a lone battle, but that the whole medical profession, and particularly the nursing profession, will speak with one voice, and will tell the mandarins of Portland Place that tradition and individuality still count for something, and that this unique foundation must be allowed to remain as a general hospital and nurses' training school.—I am, etc.,

Sevenoaks. F. F. CARTWRIGHT.

SIR,—As Chairman of the Medical Committee of St. John's Hospital, Lewisham, I want to fully endorse and support Mr. H. P. Winsbury-White's letter (*Journal*, October 2, p. 811). I would like to report that it is not only the urological department at St. John's which is threatened. The regional board is pressing for the E.N.T. unit of 11 beds, both in- and out-patients, to be transferred to the Park Hospital, two miles away. This will mean that one more specialty will be removed from St. John's, jeopardizing as it will our well-known training centre for nurses, as we shall not have enough nursing staff to second them.

This contemplated action will deprive the people of Lewisham, and the local practitioners, of a service which has existed for over 30 years. The Park Hospital is primarily a fever hospital and lacks a great many of the facilities necessary for E.N.T. work. Consultations with other specialists will be considerably restricted, and in most cases will entail patients travelling to other hospitals and waiting their turn, perhaps for weeks, for an appointment. There is only one bus route which serves this isolated hospital.

At present, St. John's Hospital is attracting the very best type of junior house officer; this is because all specialties are treated at the hospital, and instruction is given by the various specialists. I feel confident that it will cease to attract the best type of men if these changes are implemented.—I am, etc.,

CHARLES BENEY,
Chairman, Medical Committee,
St. John's Hospital, Lewisham.

Photographs Wanted

SIR,—I am endeavouring to make a collection of photographs of former apothecaries of this hospital, and have been unable to obtain those of any of the following. The dates refer to their period of office here: John Hogg, 1828–34; John Taylor, 1834–41, later Professor of Medicine, University College Hospital, and physician to Huddersfield Royal Infirmary; Charles Percy Croft, 1846–8, later one of the founders of the Royal (formerly Great) Northern Hospital; Thomas Hillier, 1853–6, later physician to the Hospital for Sick Children, Great Ormond Street; William Price Jones, 1856–9; Edwyn Andrew, 1859–61, later a founder of the Shropshire and Northern Wales Eye and Throat Infirmary; Charles Edward Squarey, 1866–8, later physician to the Hospital for Women and Marylebone Dispensary.

If any of your readers could lend me photographs or portraits which I could have copied I should be most grateful.—I am, etc.,

T. D. WHITTET,
Chief Pharmacist,
University College Hospital, London, W.C.1.

Obituary

A. W. FALCONER, C.B.E., D.S.O., M.D., LL.D. F.R.C.P.

Dr. A. W. Falconer, principal and vice-chancellor of the University of Capetown from 1938 to 1948, died on September 26 at the age of 74.

Arthur Wellesley Falconer was born at Stonehaven, Scotland, on May 9, 1880, and was educated at Aberdeen University, continuing his studies in London, Vienna, and Berlin. After graduating M.B., Ch.B. in 1901, he held the appointments of house-physician and house-surgeon at Aberdeen Royal Infirmary and house-physician at the Royal Infirmaries at Bradford and Bristol before settling in practice at Aberdeen, where he became honorary assistant physician to the Royal Infirmary and, later, assistant to the professor of medicine in the university. He proceeded to the M.D., with honours, in 1907, the year in which he was elected M.R.C.P. He was admitted F.R.C.P. in 1938. Falconer served in the first world war as a lieutenant-colonel in the R.A.M.C. and became consultant physician to the British Forces in Salonika. For his war services he was awarded the D.S.O. in 1918 and appointed C.B.E. in the following year. In the last war he held the rank of honorary colonel in the Active Citizen Force of the South African Medical Corps.

When Falconer was appointed to the chair of medicine in the University of Capetown in 1920 he became the first professor of medicine in South Africa. In addition to his professorial duties he acted as physician to the New Somerset Hospital at Capetown. His writings were chiefly on diseases of the heart and blood vessels and on malaria. He was a good teacher, laying stress on the value of accurate diagnosis. His later work as principal and vice-chancellor of the university from 1938 to 1948 did much to consolidate the rapid advances made by the university since its foundation in 1918. He was succeeded as principal and vice-chancellor by Dr. T. B. Davie, who was for some years George Holt professor of pathology in the University of Liverpool.

A member of the British Medical Association for many years, Falconer served as one of the honorary secretaries of the Section of Neurology and Psychological Medicine when the Association held its Annual Meeting at Aberdeen in 1914; and in South Africa from 1935 to 1937 he was both president of the Cape Western Branch and chairman of the Capetown Division. He was elected an honorary Fellow of the Royal Society of Medicine in 1942. Both Aberdeen and Capetown recognized the value of his contributions to the advancement of medical education by conferring upon him the honorary degree of LL.D.—Aberdeen in 1941 and Capetown in 1948, the year in which he retired.

A. M. SHERIDAN, O.B.E., M.B., F.R.C.S.Ed.

The death occurred suddenly on October 3, from coronary thrombosis, of Lieutenant-Colonel A. M. Sheridan, who after the abolition of the Indian Medical Service was an officer of the Ministry of Pensions and National Insurance at Queen Mary's Hospital, Roehampton. He was 53 years of age.

Arthur Manus Sheridan was born on June 26, 1901, the son of the late Mandy Sheridan, of Glasgow, and his wife Catherine. He received his professional education at Glasgow University and the Anderson College of Medicine, graduating M.B., Ch.B. in 1923. After completing an appointment as house-surgeon at Greenock Royal Infirmary, he held various resident appointments at Devonport and Nottingham, and after a short period in general practice and a year as a ship surgeon was appointed to a permanent commission in the Indian Medical Service in April, 1929. As was obligatory, his early service was spent in military employment, mainly in the Deccan, where he attracted attention by his aptitude for surgery and his interest in laboratory work. Surgery won; and in consequence of his ability in that direction he was selected for civil duties and appointed civil surgeon, Coorg, a small but independent civil surgeoncy which gave full scope to his ability and initiative both in surgery and in gynaecology and obstetrics, in which he rapidly acquired a reputation.

After a period of home leave in which he obtained the F.R.C.S. of Edinburgh, he was permanently assigned to the civil cadre of the United Provinces, where he held various civil surgeoncies, including the coveted posts of civil surgeon Lucknow and Naini Tal. In these appointments he fully justified his early promise as a surgeon and accoucheur, and established a reputation which extended throughout the province and beyond. In addition to a high degree of professional skill, which had its foundation in scrupulous attention to detail, he brought to his work keen observation, sound judgment, robust common sense, and a sense of humour which did much to support him and endeared him to his patients.

Being in "residual" posts on and after the outbreak of the late war, he was frustrated in his ambition of active service and allotted the harder task of keeping the civil medical service going, which meant always double and sometimes treble the amount of work normally entailed in the positions he held. These exacting duties, which earned him the O.B.E., he discharged with indefatigable energy and zeal; and only those closest to him knew with what envy he regarded his more fortunate juniors when they were recalled to military service which was denied to him. In 1946, when the war was over, he came home on leave, and when the end of the Indian Medical Service was in sight he retired and, after a short period in general practice, joined the Ministry of Pensions, to which service he brought all the attributes which had gone to make his career in the I.M.S. one of such distinction and promise.

Sheridan was a fine doctor, a surgeon of great skill and judgment, and a most lovable man, and his death will be widely mourned by those, both Indian and British, whom he served so unstintingly, and by a wide circle of friends of both races. He married, in 1932, Theodora, daughter of Major-General Sir Cuthbert Sprawson, C.I.E. (then Surgeon-General, Madras, and later Director-General, I.M.S.), and the late Lady Sprawson. The warm sympathy of all who knew him will go out to his widow and two sons in their tragic bereavement.—J. B. H.

D. S. McK. writes: The sudden death of Lieutenant-Colonel A. M. Sheridan has come as a great shock to his colleagues in the Artificial Limb Service of the Ministry of Health. When national self-determination brought his

distinguished career in India to an end, "Sherry" turned his talents and surgical experience to prosthetic work with quiet enthusiasm and characteristic efficiency. His unassuming and gentle ways concealed the underlying Scottish stubbornness with which he met anything which he felt to be unjust or to be against the interests of his patients or colleagues. Typical of the man is that none of us knew of the illness that led to his death and that he continued his work until the day before the end. By his loss we are the poorer. To his widow and family we extend our sympathy.

DAVID FETTES, C.B.E., M.B., F.R.C.S.Ed.

J. H. writes: The thoughts of many colleagues and former patients of this well-known and much-respected Army surgeon will be saddened at the news of his death (recorded in last week's *Journal*, p. 877). He took up surgery shortly after the end of the first world war, and devoted his time, talents, and energy to it for the rest of his life. Awarded the Montefiore Prize in surgery in 1928, he received the Leishman Memorial Medal ten years later. A considerable part of his work was done in India, notably at Rawalpindi in the interwar years. He was consulting surgeon to the British Forces in Persia and Iraq from 1941, and became consultant to the Army at the War Office in 1945. In this appointment he was engaged strenuously in the frustrating task of maintaining a satisfactory service for the Army and its dependants in surgical and allied specialties in the face of the quick return to civilian life of members of the fine teams that had been built up with success during the 1939–45 war. Fettes strove hard and maintained high standards. Among other achievements, he was instrumental in improving the education of Army surgeons and in establishing effective liaison between the Queen Alexandra Military Hospital, Millbank, and the Westminster Hospital, by which facilities for radiotherapy were provided.

After spending a year as surgical consultant with the occupational forces in Germany, Brigadier Fettes retired from the Army in 1950. He settled near Weymouth and was happy working as a consultant to a group of hospitals in Dorset until his last illness overtook him. His nonchalant fortitude throughout the course of his malady, the nature of which he knew all too well, was a fine example to everyone.

Fettes was an able clinician. His experience, gained in a hard field, particularly in the varied facets of tropical conditions, was wide and his judgment calm and balanced. His operative skill was scrupulous and good. All his patients were individual problems to him and he was painstaking in explanation to them or their relatives. Gifted with a lucid pen, he had the power of leadership by integrity and example. He was a patient, sensible, and candid counsellor to his juniors and never afraid to accept their failures. Above all, he was loyal to his service, to the Army, and to surgery. The lives of many of us have been enriched by knowing him and having his friendship. His memory will long remain as an inspiration. Our sincere sympathy is tendered to his widow and son.

ALFRED COX, O.B.E., M.A., LL.D., M.B.

Dr. A. Simpson Wells writes from Capetown: After reading the fine tributes to the memory of Dr. Alfred Cox it occurred to me that as we owed so much to him in the old days a reference should be made to his visits to South Africa. He gave great help to our Branches of the B.M.A. and guidance in the formation of our South African Medical Association, still affiliated to what we used to call "our parent body." We held him in high esteem here. Led by a member of our profession whom we now know as General Orenstein, members of our Branch in Johannesburg presented him with a cigarette case (said to have been made of pure gold) with the legend "Thank you, Cox" engraved on it. He used to take pleasure in handing it to friends, when he observed their surprise at its weight. It was symbolic of the man.

Mr. R. R. S. Bowker, who died at his home at Newport, Monmouthshire, on September 25 at the age of 58, was the last of a line of medical men. His father, Dr. Charles Stancer Bowker, who died in 1937, was for forty years a well-known and successful practitioner at Pontnewydd, Monmouthshire, and his grandfather, Dr. Robert Stancer Bowker, was in practice in the Midlands. His elder brother died in the Gold Coast soon after the end of the first world war. Richard Ryther Stancer Bowker was born at Pontnewydd on January 7, 1896, and was educated at Denstone College, where he showed great promise. He then went as a very young student to read medicine at Glasgow University, but the first world war intervened and he joined the Royal Navy as a surgeon-probationer and served in H.M.S. *Heligon* at the Battle of Jutland under Admiral Jellicoe. After the war he returned to his studies and graduated M.B., Ch.B. in 1920. He was never in love with the idea of following his father in general practice, so, after holding the appointments of house-surgeon at Queen's Hospital, Birmingham, and house-physician at the Western Infirmary, Glasgow, he came to London to study anatomy and surgery, and later went to Vienna, where he obtained a diploma in urogenitary surgery. He took the F.R.C.S.Ed. in 1926, and was appointed assistant surgeon to the Royal Gwent Hospital, Newport, in the following year, becoming a full surgeon in 1929 and ultimately senior surgeon. His success was never in doubt, and it was not long before he was appointed, in an honorary capacity, to the staffs of the Pontypool, Oakdale, and Crickhowell hospitals. Later he became a consultant surgeon to the Welsh Regional Hospital Board under the National Health Service. He was a very hard worker, and in his early days at Newport did a large proportion of the emergency surgery in the surrounding area, never being called on in vain. Administrative work did not appeal to him, and he did not make friends easily—his main interests, apart from his work, being reading, horticulture, and fishing. There was nothing he loved more than to have a few quiet hours in a trout stream among the beautiful Breconshire hills. He retired because of ill-health in March last year. He is survived by his widow and his sister, to whom our sincere sympathy is extended.—J. P. J.

Bournemouth has lost another prominent medical practitioner by the death on September 30, within a few days of his 86th birthday, of Dr. Anthony McCall, consulting surgeon to the throat, nose, and ear department of the Royal Victoria and West Hants Hospital. Anthony McCall was born at Ayr on October 5, 1868, and was educated at Ayr Academy and at Glasgow University, where he graduated M.B., C.M., with commendation, in 1889. After graduation he held the appointment of assistant in the physiology laboratory at Glasgow University, and then continued his studies in Vienna, where he assisted Professor Politzer. In 1890 he settled in general practice at Conisborough, Yorkshire, becoming physician and surgeon to the Mexborough Cottage Hospital. He also held the appointment of medical officer to the now almost forgotten Manchester, Sheffield, and Lincolnshire Railway, continuing in that capacity when the line was merged in the old Great Central Railway, and to a number of friendly societies. He left Conisborough for Boscombe in 1899, the year in which he proceeded to the M.D., to specialize in diseases of the ear, nose, and throat, work which had always had a particular appeal to him. His first appointment at Boscombe was that of honorary medical officer to the Charlotte Home for Convalescents, but he soon joined the staff of the Royal Boscombe (now Royal Victoria) and West Hants Hospital as surgeon to the throat, nose, and ear department. About this time he became a Fellow of the British Laryngological, Rhinological, and Otological Association and the Otological Society of the United Kingdom, before these bodies amalgamated with others to become the Royal Society of Medicine in 1907. He eventually became senior surgeon to the department at the Royal Victoria, and when he retired he was appointed consulting surgeon. A member of the British

Medical Association for 63 years, he was honorary secretary of the Dorset and West Hants Branch for the exceptionally long period of 26 years (from 1923 to 1948) and was chairman of the Bournemouth Division in 1929–30. When the Association held its Annual Meeting at Bournemouth in 1934 he served as a vice-president of the Section of Oto-rhino-laryngology, and he contributed to the success of the Annual Meeting as a whole as one of the local representatives on the Arrangements Committee. From 1915 to 1917 he was president of the Bournemouth Medical Society.

Medico-Legal

DEATH AFTER TRANSFUSION OF INFECTED BLOOD

On September 20, 1954, a 20-year-old girl who was receiving treatment at Black Notley Hospital for advanced bilateral pulmonary tuberculosis underwent an operation for removal of part of her left lung. Four pints (2.3 litres) of blood and one pint (0.6 litre) of dextran were administered during and after the operation, and the patient's convalescence was as satisfactory as could have been expected. On September 25 it was decided that a further blood transfusion was necessary, and this was started at 10.10 a.m. with blood of the same group as the patient's. Within eight minutes, after about one ounce (28 ml.) of blood had been run in, a reaction occurred which consisted of sweating, shivering, generalized abdominal pain, vomiting, and cyanosis. The blood transfusion was stopped, but in 10 minutes the patient became unconscious. She regained consciousness five minutes after an injection, but the pulse rate increased and the blood pressure fell, and the patient died on September 26, 22 hours after the transfusion was started. Giving evidence at the inquest on September 30 Dr. J. W. Lacey, consultant pathologist, said that he had carried out the post-mortem examination on this patient and found the cause of death to be (1) peripheral circulatory failure, (2) administration of infected blood, and (3) lobectomy for chronic phthisis. Dr. J. S. B. Greenfield, senior hospital medical officer at Black Notley Hospital, after describing the course of the patient's illness, said that after her collapse it was learned from the laboratory that the blood being used for the transfusion was infected, numerous Gram-negative encapsulated bacilli having been found in it. As soon as this was known treatment was begun with aureomycin and terramycin, but this was ineffective. The blood must have been infected before it reached the hospital, and in Dr. Greenfield's opinion the infected blood accelerated this patient's death, though she was seriously ill from tuberculosis and the effects of the operation.

The Coroner, Dr. J. F. Macdonald, remarked that the death of this patient was due to an accident which rarely happened, and a verdict of death by misadventure was recorded.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Dr. C. C. D. Shute has been reappointed a University Demonstrator in the Department of Anatomy.

UNIVERSITY OF LEEDS

The following candidates have been approved at the examinations indicated:

M.D.—R. A. Holman.

M.B., Ch.B.—Jean W. Bentley, E. H. Burrill, Helen Clarke, E. V. Dulson, J. E. H. Ellis, J. R. P. Gibbons, R. H. Grainger, G. G. Haigh, J. B. Haigh, Margaret A. Harrison, Angela Kilbride, Audrey J. Lacey, W. E. Mellor, W. P. Mitchell, S. C. Noble, W. J. Price, Pamela Raine, H. L. Roberts, G. Robinson, R. A. Surtees, A. N. Watson, C. Watson, F. Weston.

Diploma in Psychological Medicine.—*Part I:* Agnes D. Collins, Dorothy J. Galbraith, F. Lake, V. N. Stevenage, I. C. Wilson.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 25** (No. 38) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	8	0	1	0		20	3	6	0	
Dysentery	308	35	133	8		205	43	94	8	10
Encephalitis, acute	4	0	0	0		5	1	1	0	
Enteric fever:										
Typhoid	2	0	0	0	0	9	0	1	2	0
Paratyphoid	11	1	1(B)	0	6(B)	11	1	3(B)	1	1(B)
Food-poisoning	265	22		1		256	24		1	
Infective enteritis or diarrhoea under 2 years				18	18				19	59
Measles*	1,415	80	163	12	24	802	27	30	21	30
Meningococcal infection	21	1	5	0		26	2	6	0	3
Ophthalmia neonatorum	37	2	6	0		27	1	4	0	
Pneumonia†	251	11	80	5		183	12	119	6	1
Poliomyelitis, acute:										
Paralytic	49	1	22	4	3	123	9	26	10	16
Non-paralytic	35	3				101	7			
Puerperal fever§	212	33	9	0		246	38	11	0	
Scarlet fever	526	35	80	25	34	483	26	123	13	26
Tuberculosis:										
Respiratory	694	68	123	23	0			131	22	
Non-respiratory	92	6	24	2	0			19	6	
Whooping-cough	1,566	84	104	14	16	4,058	354	516	28	65

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		1	1		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	1	1	2	6	2	0	0	0
Influenza	4	0	0	0	0	0	0	0	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	3				0	0		
Pneumonia	137	15	15	7	5	115	14	17	10	3
Poliomyelitis, acute	2	0	1		0	8	0	1		0
Scarlet fever		0	0	0	0		0	1	0	0
Tuberculosis:										
Respiratory	63	8	5	3	5	84	14	8	1	3
Non-respiratory		1	6	0	1		1	1	0	1
Whooping-cough	1	0	0	0	0	2	0	0	0	0
Deaths 0–1 year	192	24	25	11	15	162	31	22	4	9
Deaths (excluding stillbirths)	4,673	680	542	110	178	4,146	595	490	99	107
LIVE BIRTHS	7,249	1066	861	181	444	7,289	1081	786	200	385
STILLBIRTHS	209	23	24			185	25	30		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

The largest variations in the number of notifications of infectious diseases in England and Wales during the week ending September 25 were rises of 129 for measles, from 1,286 to 1,415, 100 for scarlet fever, from 426 to 526, and a fall of 102 for whooping-cough, from 1,668 to 1,566.

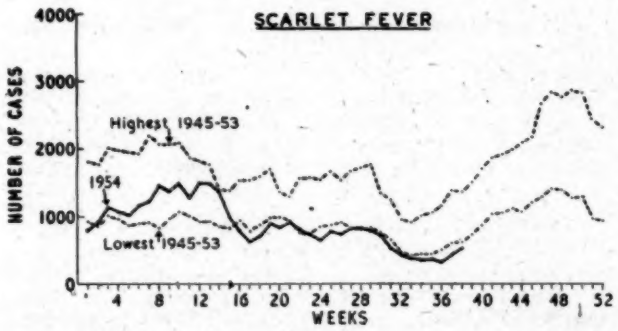
The only large fluctuations in the local trends of measles were a rise of 64 in Lancashire, from 508 to 572, and a fall of 45 in Durham, from 159 to 114. Only small variations were recorded in the local trends of scarlet fever. The variations in the returns of whooping-cough were small with the exception of a decrease of 88 in Lancashire, from 265 to 177. 8 cases of diphtheria were notified, being 1 fewer than in the preceding week.

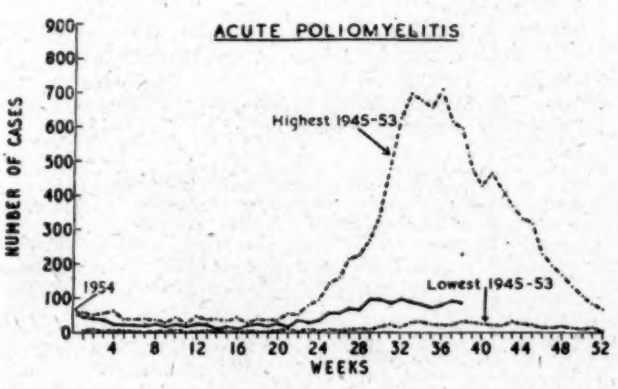
84 cases of acute poliomyelitis were notified during the week, and these were 9 fewer for paralytic and 1 more for non-paralytic cases than in the preceding week. The largest returns were Durham 12 (South Shields C.B. 3, Blaydon U.D. 3, Felling U.D. 3), Yorkshire West Riding 9 (Leeds C.B. 2, Selby R.D. 2), Yorkshire East Riding 8 (Kingston upon Hull C.B. 5, Haltemprice U.D. 2), Warwickshire 5 (Birmingham C.B. 2), and Lancashire 5 (Liverpool C.B. 3).

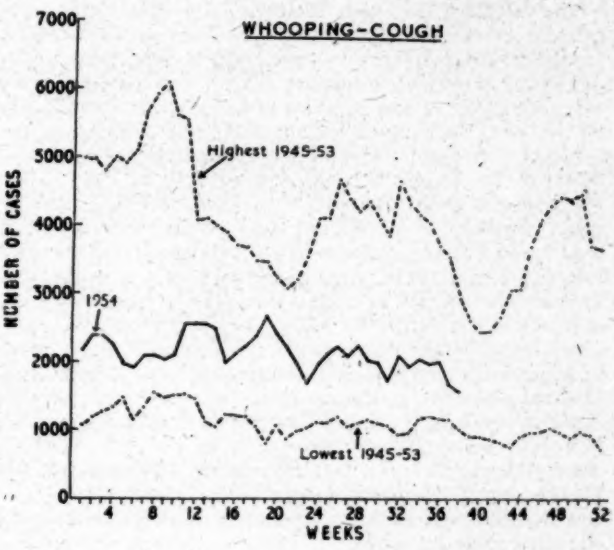
308 cases of dysentery were notified during the week, and the total was 1 fewer than in the preceding week. The chief centres of infection were Surrey 60 (Barnes M.B. 26, Banstead U.D. 25), Yorkshire West Riding 44 (Bradford C.B. 10), Lancashire 35, London 35 (Islington 11), and Warwickshire 16 (Nuneaton M.B. 11).

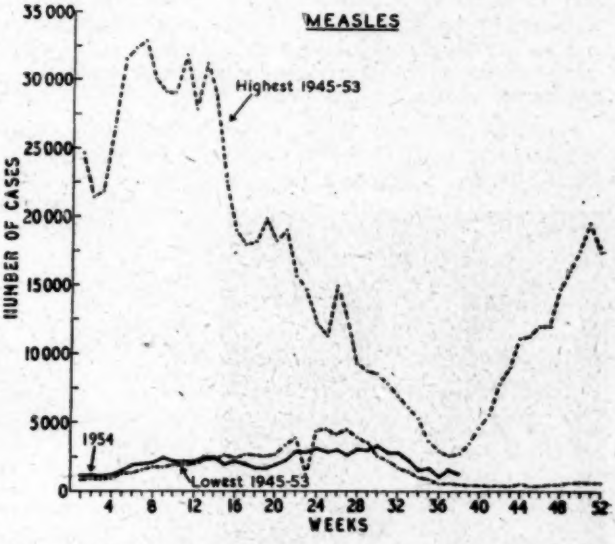
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending October 2

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 546, whooping-cough 1,464, diphtheria 11, measles 1,833, acute pneumonia 324, acute poliomyelitis 70, dysentery 369, paratyphoid fever 7, and typhoid fever 6.

Medical News

Tetracycline, Aureomycin, and Terramycin.—From October 15 tetracycline will be available to N.H.S. hospitals, and also to general practitioners through the same distribution centres and under the same arrangements as for aureomycin and terramycin. Tetracycline will be dispensed in forms suitable for both oral and parenteral administration, and there will be oral preparations specially suitable for young children. The Medical Research Council has advised the Ministry of Health that the indications, toxicity, and necessary precautions are the same for tetracycline as for aureomycin and terramycin. On November 1 the last two antibiotics will be generally available on prescription, both on Form E.C.10 and outside the Health Service. A statement from the Medical Research Council on the use of aureomycin and terramycin will be printed in next week's *Journal*.

The Medical Research Worker.—An important international conference on the selection, training, and support of medical research workers was held in London last week at the Royal Society of Medicine. Its primary object was an exchange of views and experience, but after the publication of the promised volume summarizing the discussions the conference may well prove to have far-reaching results. The initiative for calling the conference lay with the Council for International Organizations of Medical Sciences, a body under the auspices of W.H.O. and Unesco with its headquarters in Paris. The council invited central and national research organizations from many parts of the world each to send one or two delegates with special experience; Sir HAROLD HIMSWORTH, secretary of the Medical Research Council, was appointed chairman. The result was a small and particularly well-informed meeting, which sat from October 4 to 8. Delegates came from medical research organizations in Australia, Belgium, Canada, Germany, Holland, India, Ireland, Israel, New Zealand, Norway, South Africa, Sweden, Switzerland, the United Kingdom, the United States, and Yugoslavia; and others had been invited. The discussions ranged over subjects such as the recruitment and training of research workers, the integration of research in universities with research elsewhere, methods of supporting research, careers in medical research, and various aspects of international co-operation. A summary account of the concluding session will appear in a later issue.

Memorial to York Surgeon.—At a service in York Minster on October 11 the Dean of York, the Very Rev. E. MILNER-WHITE, dedicated a panel in the choir screen "In grateful memory of the merciful work of the surgeons and physicians of York through the centuries, and of Arthur Hedley Visick, surgeon, 1897–1949." It is believed to be the first memorial of its kind in any cathedral in this country, and is the first of a series of similar panels which will commemorate the work and representatives of other professions and callings. Hedley Visick was surgeon at York County Hospital. Shortly after his death a group of his patients organized a fund which has endowed annual prizes in surgical nursing at two York hospitals, and it is the remainder of this fund that has been used for the memorial in the Minster. The memorial, which is illustrated above, is the work of Mr. H. J. Stammers, the well-known designer of stained glass and church decoration, and is unusual in that the figures are picked out almost entirely in gold. The separate figures represent The Crucifixion; St. Luke the Beloved Physician; St. Peter and St. John healing the lame man; Rahere, the Jester who founded St. Bartholomew's Hospital; Florence Nightingale; and Alcuin, who planned St. Peter's Hospital, York, *circa* A.D. 796.

Scottish Hospital Endowments Research Trust.—Sir JOHN ERSKINE, chairman of the trust, gave a Press conference on October 6 in Edinburgh at which he said that the trust was now ready to start operating. At the moment the annual income was £20,000, but by the end of next year it was hoped that the amount would be in the region of £100,000. This money would be used to promote medical research in Scotland. Sir EDWARD APPLETON, F.R.S., Principal of Edinburgh University, and until a few days ago chairman of the Advisory Committee on Medical Research in Scotland, also spoke at the conference. A note about the trust was printed in the *Journal* earlier this year (January 16, p. 163).

Epsom College.—Mr. RONALD RAVEN, F.R.C.S., and Brigadier H. LL. GLYN HUGHES, Q.H.P., have been appointed respectively chairman and vice-chairman of Epsom College. They succeed Dr. H. SPITTA and Sir ERNEST GOODHEART, Bt.

Clinical Research Board.—Dr. W. P. SHELDON, physician to the Hospital for Sick Children, Great Ormond Street, has been appointed to the board in the place of the late Sir JAMES SPENCE.

COMING EVENTS

Albert Schweitzer Exhibition.—Photographs by Erica Anderson taken at Dr. Schweitzer's hospital in equatorial Africa on show at the Kodak Gallery, 184, Regent Street, London, W.1, October 15–30.

Varicose Ulcer Clinic.—Sir ARTHUR PORRITT will open a new varicose ulcer clinic at the Battersea Central Mission, York Road, London, S.W.11, on October 20, at 8 p.m.

Society of Anaesthetists of South Wales.—Annual dinner meeting at the Park Hotel, Cardiff, October 21, at 7.30 p.m. Professor W. W. MUSHIN will speak on "An Anaesthetist in Brazil."

Edinburgh Clinical Club.—Dr. WILLIAM PICKLES will speak on "Epidemiology" on October 21 at 8 p.m. at the B.M.A. Rooms, 7, Drumsheugh Gardens.

Postgraduate Orthopaedic Course.—Arranged by the British Orthopaedic Association, on October 21 at the Royal College of Surgeons, Lincoln's Inn Fields, starting at 10.30 a.m. Subjects: "The Knee Joint," "The Principles of Hand Surgery," "Traumatic Paraplegia," and "Cervical Disks." Open to all doctors interested.

British Orthopaedic Association.—London meeting, October 21–23, at the Royal College of Surgeons, Lincoln's Inn Fields.

Soviet Medicine.—Members of the medical party which visited Russia recently (see *Journal*, October 2, p. 863) will describe their impressions and answer questions at a meeting of the medical section of the Society for Cultural Relations with the U.S.S.R. on October 22 at 8 p.m. at the Royal College of Surgeons, Lincoln's Inn Fields. Dr. H. JOULES will be in the chair. The meeting is open to any member of the medical profession.

Postgraduate Courses at Cambridge.—Details of one-day symposia (10.30 a.m.–5 p.m.) at Cambridge University Medical School, arranged for general practitioners, may be obtained from the secretary, the Medical School, Tennis Court Road, Cambridge. The courses are held on Saturdays, beginning on October 23.

University College Hospital Medical School.—Annual dinner at the Savoy Hotel, London, on October 29. Tickets, price 30s., from the Dinner Secretary, U.C.H. Medical School, University Street, London, W.C.1. Postgraduate demonstrations will be held on October 28 and 29.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, October 16

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Children's Clinic, Farnborough Hospital, Kent, 3 p.m., Dr. J. R. Rees: Mental Health of Children—A Trans-National Viewpoint.

Monday, October 18

HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, E.C., 7 for 7.30 p.m., dinner meeting. Presidential address by Dr. W. S. C. Copeman: Twenty-five Years a Hunterian.

●INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. J. P. Martin: Disorders of Ocular Movement of Nuclear and Supra-nuclear Origin.
INSTITUTE OF PSYCHIATRY.—5.30 p.m., lecture-demonstration by Dr. E. Stengel.

Tuesday, October 19

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At Beveridge Hall, Senate House, W.C., 5.30 p.m., Professor A. V. Hill, F.R.S.: Why Biophysics?
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. E. J. Moynahan: Urticaria.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Erasmus Wilson Demonstration by Dr. B. E. Heard: Effect of Very Low Temperature on Living Tissue.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. G. D. Read: Preparation for Labour.
SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., Dr. J. S. Heller: Reversible and Irreversible Pathological Changes Produced by Excessive Consumption of Alcohol.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, Wandsworth Common, S.W., 8.30 p.m., Dr. Michael Kremer: Pain in the Upper Limb.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Nervous Disease (Part II).

Wednesday, October 20

EUGENICS SOCIETY.—At Burlington House, 5.30 p.m., Professor S. Chandrasekhar, Ph.D.: Infant Mortality in India: 1901-1951. A Demographic Revolution.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Diagnosis by Biopsy and Cytology.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. I. Williams: Retention of Urine in Childhood.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. H. Harris: Biochemical Genetics.
ROYAL MICROSCOPICAL SOCIETY.—5.30 p.m., Dr. J. N. McArthur: A Contribution to Microscope Design.
WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.45 p.m., discussion: Recent Advances in Plastic Surgery. Speaker, Mr. N. L. Eckhoff.

Thursday, October 21

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor B. S. Platt: Protein Malnutrition.
GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7.30 p.m., Dr. J. G. Graham: Medical Treatment of Essential Hypertension.
ILFORD MEDICAL SOCIETY.—At Cumberland Hotel, W., 6.30 for 7 p.m., annual dinner and dance. Principal guest, Lord Horder.
MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, 5 p.m. Dr. John H. Hanks (Harvard Medical School): Application of Metabolic Study to Leprosy Research.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Mr. A. G. Riddell: Ammonia Intoxication in Surgical Patients.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Bengué Memorial Award Lecture by Dr. Frankis T. Evans: The Veins and the Anaesthetist.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26, Portland Place, W., 7.30 p.m., Dr. R. B. Heisch: Epidemiology of an Outbreak of Kala-azar in Kenya. A discussion will follow.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: Neurology demonstration.
SOCIETY OF ANAESTHETISTS OF SOUTH WALES.—At Park Hotel, Cardiff, dinner meeting. Professor W. W. Mushin: An Anaesthetist in Brazil.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Rembrandt Hotel, S.W., 7.15 for 7.30 p.m., Presidential address by Dr. W. R. Thrower: The Journey from the Bench to the Bedside.

Friday, October 22

BRITISH ASSOCIATION OF ALLERGISTS.—At Wright-Fleming Institute, St. Mary's Hospital, 5 p.m., general meeting, clinico-pathological discussion: Polyarteritis.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. H. J. Wallace.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. N. C. Oswald and Mr. W. P. Cleland.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. Anthony Radcliffe: Nasal Obstruction and Nasal Catarrh.
NATIONAL ASSOCIATION FOR MENTAL HEALTH.—At William Beveridge Hall, Senate House, W.C., 5 p.m., public meeting. Dr. A. Querido (Amsterdam): Public Health and Mental Health.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Brigadier-General S. F. Seeley (U.S. Army): Advances in the Management of War Wounds of the Vascular System.
●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Professor W. A. Mackey: Indications for Surgery in Heart Disease.

Saturday, October 23

BRITISH ASSOCIATION OF ALLERGISTS.—At Wright-Fleming Institute, St. Mary's Hospital, 11 a.m., general meeting. Papers by Dr. J. Freeman and Dr. J. Pepys. 2 p.m., papers by Dr. G. A. Rose, Dr. J. Ackroyd, and Mrs. R. Augustin.
CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—10.30 a.m., Symposium: Disorders of the Blood.

Sunday, October 24

SOCIETY OF APOTHECARIES OF LONDON.—At Church of St. Mary, Aldermary (opposite Mansion House Station), 11.15 a.m., Master's Day Service.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Glyn.—On September 2, 1954, at the Middlesex Hospital, London, W., to Daphne (formerly Bayley), wife of Dr. J. H. Glyn, a daughter—Gillian.

DEATHS

Pou.—On September 21, 1954, at 55, Hove Park Road, Hove, Sussex, William Oscar Pou, M.D., D.P.H., late of Federated Malay States, aged 79.

Thomson.—On September 19, 1954, in hospital, Joseph Laidlaw Thomson, L.R.C.P.&S.Ed., L.R.F.P.S., L.D.S. R.C.S.Ed., of 18, East Morton Street, Thornhill, Dumfriesshire.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Indications for Operation on a Prolapsed Disk

Q.—*What are the indications for operating on a prolapsed lumbar intervertebral disk, producing typical symptoms?*

A.—The one absolute indication for operating upon a lumbar intervertebral disk protrusion is the development of a severe neurological deficit, with paresis of muscles supplied by the sacral anterior roots, sensory loss in the distribution of the sacral posterior roots, and disturbance of sphincter control. This clinical picture is uncommon and recorded in but 1 to 2% of large series of cases subjected to operation. The other indications for operation are relative, the severity and duration of symptoms and the frequency of recurring attacks being of particular importance. The severity of pain is gauged not only from the history but also from the physical signs—spinal deformity, gross limitation of spinal movement, and marked reduction of straight leg raising indicating severe pain. Only when pain has persisted for a minimum period of three months should operation be advised in any but the most severely affected patients, except when attacks of shorter duration occur with but a few weeks' interval of freedom. In all cases—apart from those with a gross neurological deficit—the patient should have a period of bed rest of six to eight weeks before operation is advised.

Infective and Serum Hepatitis

Q.—*(a) What is the relationship of the virus causing homologous serum hepatitis to that causing infective hepatitis? (b) Why is the incubation period of homologous serum hepatitis so much longer than in infective hepatitis? (c) Do blood-sucking insects play any part in the transmission of either disease? (d) What are the chances of hepatic cirrhosis after each of these diseases?*

A.—The absence of a suitable laboratory test for these two viruses makes it difficult to give a concrete answer to some of these questions. Ideas have to be based on a limited series of experiments in human volunteers.

(*a*) The two viruses appear to be related but not identical. In terms of resistance to physical and chemical agents they seem to be similar, and also from the clinical aspect, except that the onset of infective hepatitis is usually less insidious and more often accompanied by fever than in serum hepatitis. The most marked differences are in the length of the incubation periods, the routes of infection, mode of transmission, and in the immune response. Serum hepatitis (SH or virus B) is transmitted by parenteral inoculation of infected blood. Infective hepatitis (IH or virus A) can be transmitted by infected blood, but contact infection from infected excreta is more common. In this respect infective hepatitis is not unlike poliomyelitis.

(*b*) The reason is not known. Virus B (SH) can apparently exist in the blood for long periods without causing symptoms or disease, and in this respect it is not unlike other animal viruses such as psittacosis virus, which persist in a silent form. Immunity to virus B (SH) appears to be less effective than in the case of virus A (IH).

(*c*) It is theoretically possible that blood-sucking insects may play a part in transmission, but there is no information on this point. Certainly in Britain insect vectors are not likely to be of significance.

(*d*) Again no reliable information is available. The effect of the two forms is about equal, though it has been

suggested that serum hepatitis is the more severe. The chances of cirrhosis in a previously healthy subject are probably in the region of 0.5–1%, but this figure may be higher after subsequent attacks.

Oil at Work

Q.—*I have a patient whose normal work is that of machine-tool setter, but he has developed what appears to be a sensitivity to the oil used. He was put on another job for eight months, but the condition recurred as soon as he returned to his original work. Is there any means of either desensitizing this patient or otherwise protecting him against the oil? What is the legal position in regard to a claim for compensation?*

A.—The question does not state what form the sensitivity to the oil took. One may assume that it was a form of contact dermatitis—that is, an erythematous or eczematous reaction in the areas of skin contaminated by the oil. Even this association and the recurrence on return to tool-setting are not, of course, proof that the oil was responsible; on occasion, for example, men who work in oil use over-drastic forms of cleansing (sometimes including strong disinfectants) and produce acute skin irritation in this way. Direct incrimination of the oil is possible by application of test patches after subsidence of the rash, using dilutions initially—for example, 1:100 of the oil in liquid paraffin—and full-strength oil only if this gives a negative result.

Oil itself is seldom a sensitizing agent. Its effect on the skin is usually to produce a folliculitis by action on the sebaceous follicles. Modern cutting oils, however, often contain additives, which may be skin irritants or sensitizers. Sometimes overheating of oil produces irritating degradation products. Each situation therefore requires detailed investigation. Desensitization is usually out of the question. Personal protection of forearms with "oil-sleeves," and the body with an apron, is often useful, especially for the control of folliculitis. Protection of the hands, if these tend to be involved in an acute skin reaction, is not feasible, since barrier creams are readily penetrated by oils, and gloves cannot be used for fine work like tool-setting.

Oil dermatitis is a prescribed disease under the Industrial Injuries Act, 1946. It may therefore attract injury benefit for incapacity for work and for disablement benefit for "loss of faculty" after the injury benefit period is over. For a person whose loss of faculty causes financial loss there is available an additional benefit termed Special Hardships Allowance. Full details and leaflets about these benefits are available on request at all offices of the Ministry of Pensions and National Insurance.

Contraindications to Phenylbutazone

Q.—*What are the contraindications to phenylbutazone? Is a regular blood count an essential precaution when using this drug, and, if so, how often should it be done and what should it consist of?*

A.—In a certain number of patients phenylbutazone appears to exert a powerful analgesic effect, but in many the dosage required to produce this causes undesirable and even dangerous toxic complications. The incidence of these complications has been as high as 30–50% in most published series. The main toxic effects are malaise, fever, skin rashes, and sore throat, occasionally accompanied by agranulomatosis, which may be fatal; oedema from salt retention, which may precipitate cardiac failure; dyspepsia, occasionally accompanied by gastric bleeding which may be serious; and disturbance of blood clotting.

The main contraindications to the use of phenylbutazone are: leucopenia, or known idiosyncrasy to drugs; reduced cardiac or renal reserve; a history of dyspepsia or peptic ulceration, and thrombo-embolic phenomena. The incidence of complications appears to increase with age, so that this drug should generally not be given to elderly patients, particularly since renal and cardiac reserve is usually reduced in old age.

Though a white cell count should be done before starting treatment with phenylbutazone, repeated counts during treatment are of little value, since the onset of agranulomatosis is usually sudden and heralded by the onset of symptoms such as malaise and sore throat rather than by changes in the white cell count. If striking symptomatic relief is not obtained with a dosage of less than 600 mg. per day, treatment should be discontinued. All patients receiving phenylbutazone therapy should be instructed to stop the treatment immediately on the appearance of any untoward symptoms, since the drug is excreted slowly and it may take several days for both therapeutic and toxic effects to wear off.

Value of Pneumoperitoneum

Q.—*Is it established beyond doubt that artificial pneumoperitoneum has a beneficial effect in pulmonary tuberculosis? Please cite a few key references.*

A.—To establish beyond doubt that a method of treatment is beneficial usually requires a carefully designed and controlled trial. This may not be so if the results are dramatically better than anything that has gone before, as were, for instance, the results of treating tuberculous meningitis with streptomycin. But pulmonary tuberculosis is a variable disease, and we know of no carefully controlled trial of artificial pneumoperitoneum which gives an unequivocal answer to the question asked. The results reported in different series vary with the type of case treated, the criteria of success, and the length of follow-up. In certain larger series figures for "success" (variously defined) lie mainly between 30 and 60%. Reports up to 1945 are summarized by Mitchell and his colleagues,[1] who add 710 cases of their own with "satisfactory results" in 45%. Morris and Bogen[2] report a 10-year follow-up of 200 patients, 35 of whom had tuberculous peritonitis or enteritis and the rest far advanced pulmonary disease; 55% were dead and only 40% of the survivors were working. Crenshaw and Gross[3] achieved "success" in slightly under 50% of cases, mostly moderately or far advanced, apparently followed up for at least five years.

References

1 *Amer. Rev. Tuberc.*, 1947, **55**, 306.
2 *J. Amer. med. Ass.*, 1952, **149**, 1120.
3 *Dis. Chest*, 1952, **22**, 91.

Masks to Prevent Farmer's Lung

Q.—*Would a smog mask or any other filtering device protect farmers against the contraction of farmer's lung?*

A.—It is reasonably certain that farmer's lung is due to the inhalation of dust from mouldy hay or straw. The actual cause, however, is not definitely known. There is no doubt that farm workers can avoid the condition if they wear a light mask such as is used in a hospital operating theatre when they are employed on work such as threshing or feeding their cattle with mouldy hay.

Correction.—There was a misprint in D. S. R.'s appreciation of the late Dr. Marjorie Back (*Journal*, October 2, p. 817). The word "clerical" in the tenth line should have been "clinical."

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